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(71) Applicant (for all designated States except US): PFIZER
PRODUCTS INC. [US/US]; Eastern Point Road, Groton,
CT 06340 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NOE, Mark, Carl
[US/US]; Pfizer Global Research and Development, East-
ern Point Road, Groton, CT 06340 (US). FREEMAN-
COOK, Kevin, Daniel [US/US]; Pfizer Global Research
and Development, Eastern Point Road, Groton, CT 06340
(US).

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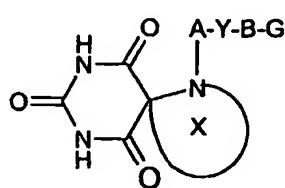
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(54) Title: N-SUBSTITUTED-HETEROARYLOXY-ARYL-SPIRO-PYRIMIDINE-2,4,6-TRIONE METALLOPROTEINASE IN-
HIBITORS



(I)

(57) Abstract: The present invention relates to N-substituted-heteroary-
loxy-aryl-spiro-pyrimidine- 2,4,6-trione metalloproteinase inhibitors of the
formula wherein ring X is a 5-7 membered heterocyclic ring, and wherein A, Y,
B, and G are as defined in the specification; and to pharmaceutical compositions
and methods of treating inflammation, cancer and other disorders.

N-SUBSTITUTED-HETEROARYLOXY-ARYL-SPIRO-PYRIMIDINE-2,4,6-TRIONEMETALLOPROTEINASE INHIBITORSBackground of the Invention

The present invention relates to N-substituted-heteroaryloxy-aryl-spiro-pyrimidine-5,2,4,6-trione metalloproteinase inhibitors and to pharmaceutical compositions and methods of treatment of inflammation, cancer and other disorders.

The compounds of the present invention are inhibitors of zinc metalloendopeptidases, especially those belonging to the class of matrix metalloproteinases (also called MMP or matrixin).

10 The MMP subfamily of enzymes currently contains seventeen members (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-18, MMP-19, MMP-20). The MMPs are most well known for their role in regulating the turn-over of extracellular matrix proteins and as such play important roles in normal physiological processes such as reproduction, development and 15 differentiation. In addition, the MMPs are expressed in many pathological situations in which abnormal connective tissue turnover is occurring. For example, MMP-13 an enzyme with potent activity at degrading type II collagen (the principal collagen in cartilage), has been demonstrated to be overexpressed in osteoarthritic cartilage (Mitchell, *et al.*, *J. Clin. Invest.*, 97, 761 (1996)). Other MMPs (MMP-2, MMP-3, MMP-8, MMP-9, MMP-12) are also 20 overexpressed in osteoarthritic cartilage and inhibition of some or all of these MMPs is expected to slow or block the accelerated loss of cartilage typical of joint diseases such as osteoarthritis or rheumatoid arthritis.

It is recognized that different combinations of MMPs are expressed in different pathological situations. As such, inhibitors with specific selectivities for individual MMPs may 25 be preferred for individual diseases.

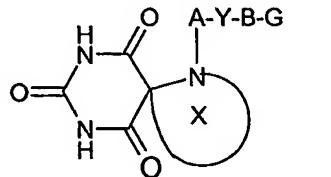
Matrix metalloproteinase inhibitors are well known in the literature. Hydroxamic acid MMP inhibitors are exemplified in European Patent Publication 606,046, published July 13, 1994. Several pyrimidine-2,4,6-trione MMP inhibitors are referred to in PCT publication WO 98/58925, published December 30, 1998. PCT publication WO 00/47565, published August 30, 2000 refers to certain aryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Non-provisional application 09/635156, filed August 9, 2000 (which claims priority to United States Provisional application 60/148547 filed August 12, 1999) refers to heteroaryl substituted pyrimidine-2,4,6-trione MMP inhibitors. United States Provisional Applications entitled "Triaryl-Oxy-Aryl-Spiro-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors"; "N-Substituted-Heteroaryloxy-Aryloxy-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors"; and "Triaryloxy-Aryloxy-Pyrimidine-2,4,6-Trione Metalloproteinase Inhibitors", all filed April 35, 2002, refer to certain pyrimidine-2,4,6-triones. Barbituric acids and methods for their

preparation are well known in the art, see for example Goodman and Gilman's, "The Pharmacological Basis of Therapeutics," 345-382 (Eighth Edition, McGraw Hill, 1990). Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

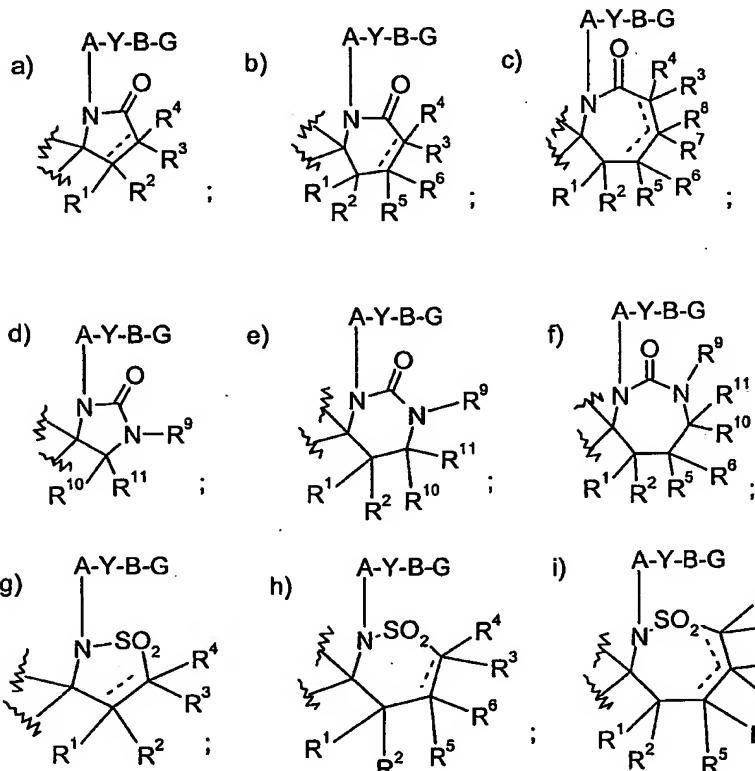
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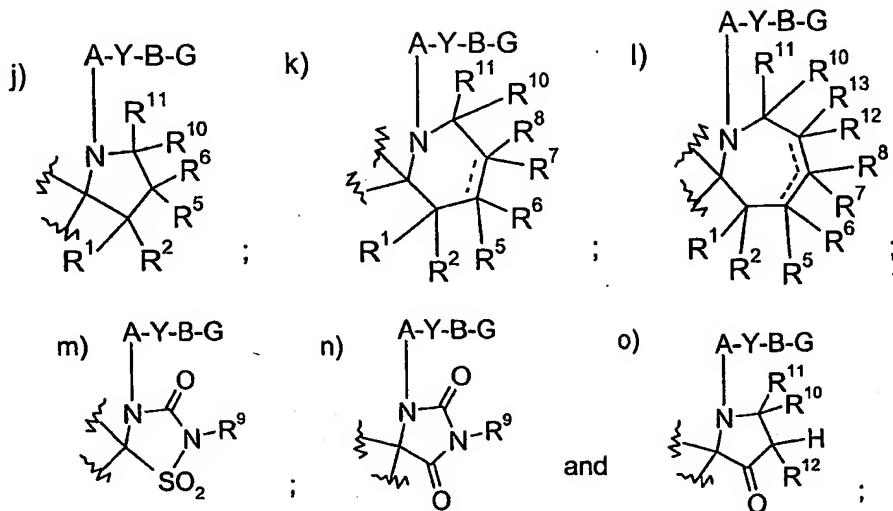
Summary of the Invention

The present invention relates to compounds of the formula:



wherein ring X is a 5-7 membered heterocyclic ring selected from the group consisting of:





wherein each dashed line represents an optional double bond;

wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ is

5 independently selected from the group consisting of hydrogen, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl;

wherein each of said R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional 10 substituent with one to three substituents per ring independently selected from halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -CN, -OH and -NH₂;

wherein each of said R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R¹³ (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may optionally be substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group 15 consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

A is (C₆-C₁₀)aryl or (C₂-C₁₀)heteroaryl;

wherein said aryl or (C₂-C₁₀)heteroaryl; may be optionally substituted on any of the ring atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy;

Y is selected from the group consisting of a bond, -O-, -S-, >C=O, >SO₂, >S=O, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂SO-, -CH₂SO₂-, -SOCH₂-, -SO₂CH₂-, >NR¹⁴, -[N(R¹⁴)]CH₂-, -CH₂[N(R¹⁴)]-, -CH₂-, -CH=CH-, -C≡C-, -[N(R¹⁴)]-SO₂- and -SO₂[N(R¹⁴)]-;

R¹⁴ is selected from the group consisting of hydrogen and (C₁-C₄)alkyl;

25 B is a heterocyclyl containing at least one nitrogen atom;

wherein one ring nitrogen atom of B is bonded to one carbon atom of G;

with the proviso that the group -B-G is not methylazetidinyl or methylpiperidinyl;

wherein said B may be optionally substituted on any of the ring atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₈)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

5 G is (C₁-C₆)alkyl or R¹⁵-(CR¹⁶R¹⁷)_p-;

 p is an integer from zero to four;

 wherein said G (C₁-C₆)alkyl may be optionally substituted on any of the carbon atoms capable of supporting an additional substituent by one to three substituents per (C₁-C₆)alkyl

10 independently selected from F, Cl, Br, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy;

 R¹⁵ is selected from the group consisting of (C₃-C₈)cycloalkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl;

 wherein each of said R¹⁵ (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy;

20 wherein each of said R¹⁵ (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl may also optionally be substituted by oxo;

 wherein each of said R¹⁵ (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl may optionally be substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C₁-C₄)alkyl and (C₁-C₄)alkyl-(C=O)-;

25 each of R¹⁶ and R¹⁷ are independently selected from the group consisting of hydrogen and (C₁-C₄)alkyl;

 or R¹⁶ and R¹⁷ may optionally be taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring;

 or the pharmaceutically acceptable salts thereof.

30 The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, para-toluenesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from 5 such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine (meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

10 The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

The compounds of the invention may also exist in different tautomeric forms. This invention relates to all tautomers of formula I.

15 The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

20 Unless otherwise indicated, the term "substituent" or "substituents" refers to a replacement of at least one atom of an individual member of a variable (R¹, R², R³ etc) of the compound of the formula I by another atom or group of atoms. For example, an (C₁-C₆)alkyl substituent may replace a hydrogen atom of R¹ (C₆-C₁₀)aryl.

Unless otherwise indicated, the term "(C₁-C₄)alkyl" or "(C₁-C₆)alkyl" as well as the (C₁-C₄)alkyl or (C₁-C₆)alkyl component of other terms referred to herein (e.g., the "(C₁-C₆)alkyl component of (C₁-C₆)alkyl-O-), may be linear or branched (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, secondary-butyl, tertiary-butyl).

25 Unless otherwise indicated, the term "halo" means fluoro, chloro, bromo or iodo.

Unless otherwise indicated, the term "(C₂-C₆)alkenyl" means straight or branched hydrocarbon chain functional groups of 2 to 6 carbon atoms having at least one double bond including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-but enyl, or 2-but enyl.

30 Unless otherwise indicated, the term "(C₂-C₆)alkynyl" is used herein to mean straight or branched hydrocarbon chain functional groups of 2 to 6 carbon atoms having one triple bond including, but not limited to, ethynyl (-C≡C-H), propynyl (-CH₂-C≡C-H or -C≡C-CH₃), or butynyl (-CH₂-CH₂-C≡C-H, or -CH₂-C≡C-CH₃, or -C≡C-CH₂CH₃).

35 Unless otherwise indicated, the term "(C₃-C₇)cycloalkyl" refers to a mono or bicyclic carbocyclic ring functional groups including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl; wherein said (C₃-C₇)cycloalkyl may optionally

contain 1 or 2 double bonds including, but not limited to, cyclopentenyl, cyclohexenyl and cycloheptenyl.

Unless otherwise indicated, the term "(C₆-C₁₀)aryl" means aromatic functional groups such as phenyl, naphthyl, tetrahydronaphthyl, or indanyl, wherein said (C₆-C₁₀)aryl is optionally substituted on any ring carbon atom by one to two sub-functional groups per ring, wherein said sub-functional groups are independently selected from the group consisting of halo, -OH, -CN, -SH, HO-(C=O)-, -NO₂, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₇)cycloalkyl, (C₆-C₁₀)aryl, (C₁-C₉)heteroaryl, (C₁-C₉)heterocyclyl, (C₁-C₆)alkyl-O-, -OCF₃, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-NH-, [(C₁-C₆)alkyl]₂-N-, (C₃-C₇)cycloalkyl-NH-, (C₆-C₁₀)aryl-NH-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-, (C₁-C₉)heteroaryl-NH-, (C₁-C₁₀)heterocyclyl-NH-, H₂N-(C=O)-, [(C₁-C₆)alkyl]-NH-(C=O)-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-(C=O)-, [(C₁-C₆)alkyl]₂-N-(C=O)-, [(C₆-C₁₀)aryl]-NH-(C=O)-, [(C₁-C₆)alkyl]-[(C₆-C₁₀)aryl]-N-(C=O)-, (C₁-C₆)alkyl-O-NH-(C=O)-, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-NH- (C₁-C₆)alkyl-(C=O)-HN-(C₁-C₆)alkyl-NH, H-(C=O)-, (C₁-C₆)alkyl-(C=O)- and (C₁-C₆)alkyl-O-(C=O)-.

Unless otherwise indicated, the term "oxo" refers to =O.

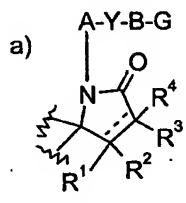
Unless otherwise indicated, the term "(C₁-C₉)heteroaryl" refers to aromatic or multicyclic functional groups wherein at least one ring of the functional groups is aromatic, wherein said aromatic or multicyclic functional groups contain one or more heteroatoms selected from the group consisting of O, S and N. The (C₁-C₉)heteroaryl functional groups can be optionally substituted by one or more oxo sub-functional groups. Examples of heteroaryl functional groups include, but are not limited to, benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any atoms capable of forming an additional bond by one or two sub-functional groups independently selected from halo, -CN, -OH, (C₁-C₆)alkyl, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkyl-O-, (C₁-C₆)alkyl-O- and (C₃-C₈)cycloalkyl-O-. Unless otherwise indicated, the foregoing (C₁-C₉)heteroaryls can be C-attached or N-attached where such is possible. For instance, pyrrolyl can be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

Unless otherwise indicated, the term "(C₁-C₉)heterocyclyl" refers to a cyclic functional groups containing 1 to 9 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of N, O and S. The heterocyclyl ring can be optionally substituted where such is possible by oxo, -CN, -OH, (C₁-C₆)alkyl, perfluoro(C₁-C₆)alkyl, perfluoro(C₁-C₆)alkyl-O-, (C₁-C₆)alkyl-O- and (C₃-C₈)cycloalkyl-O-. Examples of the cyclic functional groups include, but not limited to, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidinyl, dihydrofuranyl, dihydropyranyl, dihydrothienyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydroazepinyl,

hexahdropyrimidine, imidazolidinyl, imidazolinyl, isoxazolidinyl, morpholinyl, oxetanyl, oxazolidinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, quinolizinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl or 5 trithianyl. Unless otherwise indicated, the foregoing heterocyclic functional groups can be C-attached or N-attached where such is possible. For example, piperidinyl can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached).

Some compounds of formula I contain chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, enantiomers, diastereomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of the invention also exist in different tautomeric forms. This invention relates to all tautomers of formula I. Those skilled in the art are well aware that the pyrimidine-2,4,6-trione nucleus exists as a mixture of tautomers in solution. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular 10 crystallization technique used to isolate a compound.

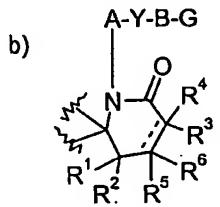
15 In one embodiment of the invention, the heterocyclic ring X has the formula a):



and wherein each of R¹, R², R³, and R⁴ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, 20 optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

In another embodiment of the invention, the heterocyclic ring X has the formula a), wherein in the heterocyclic ring X the dashed line is a double bond.

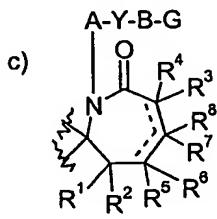
In another embodiment of the invention, the heterocyclic ring X has the formula b):



25 and wherein each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

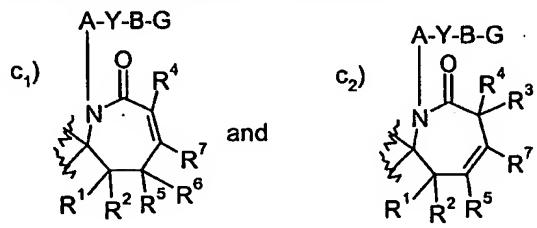
In another embodiment of the invention, the heterocyclic ring X has the formula b), wherein in the heterocyclic ring X the dashed line is a double bond.

In another embodiment of the invention, the heterocyclic ring X has the formula c):



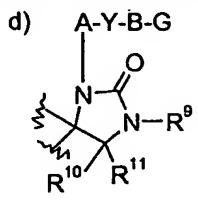
5 and wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

10 In another embodiment of the invention, the heterocyclic ring X has the formula c), wherein in the heterocyclic ring X the dashed line is a double bond, such that the heterocyclic ring X of formula c is selected from the group consisting of:



15 and wherein each of R¹, R², R³, R⁴, R⁵, R⁶, and R⁷ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

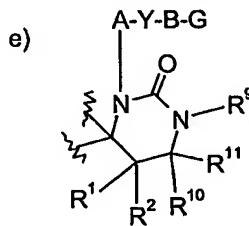
In another embodiment of the invention, the heterocyclic ring X has the formula d):



20 wherein each of R¹⁰ and R¹¹ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl; and wherein R⁹ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally

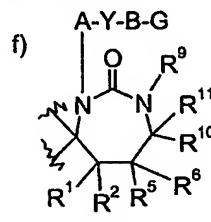
substituted (C₁-C₁₀)heterocycl; preferably R⁹ is selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

In another embodiment of the invention, the heterocyclic ring X has the formula e):



5 wherein each of R¹, R², R¹⁰ and R¹¹ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocycl; and wherein R⁹ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocycl; preferably R⁹ is selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

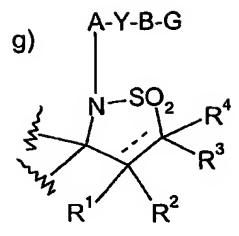
In another embodiment of the invention, the heterocyclic ring X has the formula f):



15 wherein each of R¹, R², R⁵, R⁶, R¹⁰ and R¹¹ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocycl; and wherein R⁹ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocycl; preferably R⁹ is selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

In another embodiment of the invention, the heterocyclic ring X has the formula g):

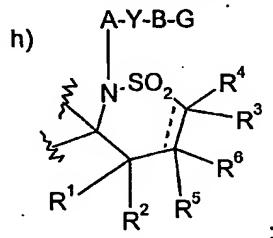
-10-



and wherein each of R¹, R², R³, and R⁴ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

5 In another embodiment of the invention, the heterocyclic ring X has the formula g), as defined in the aforesaid paragraph, wherein in the heterocyclic ring X the dashed line is a double bond.

In another embodiment of the invention, the heterocyclic ring X has the formula h):

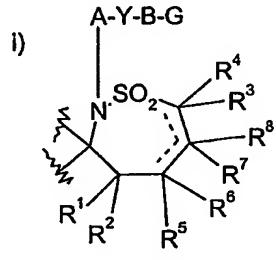


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and wherein each of R¹, R², R³, R⁴, R⁵, and R⁶ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

15 In another embodiment of the invention, the heterocyclic ring X has the formula h), as defined in the aforesaid paragraph, wherein in the heterocyclic ring X the dashed line is a double bond.

In another embodiment of the invention, the heterocyclic ring X has the formula i):

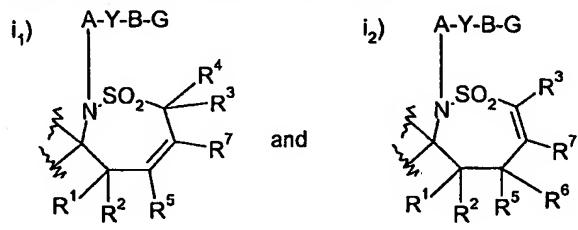


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and wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-

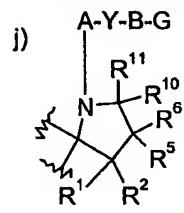
C_4)alkynyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocyclyl.

In another embodiment of the invention, the heterocyclic ring X has the formula i), wherein in the heterocyclic ring X the dashed line is a double bond, such that the heterocyclic ring X of formula i) is selected from the group consisting of:



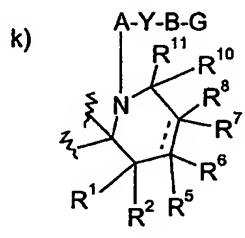
and wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 is independently selected from the group consisting of hydrogen, optionally substituted (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, 10 optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocyclyl.

In a preferred embodiment of the invention, the heterocyclic ring X has the formula j):



and wherein each of R^1 , R^2 , R^5 , R^6 , R^{10} , and R^{11} is independently selected from the group consisting of hydrogen, optionally substituted (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, 15 optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocyclyl.

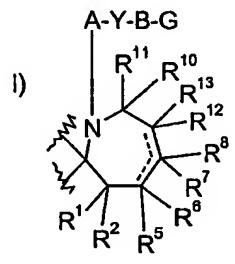
In another preferred embodiment of the invention, the heterocyclic ring X has the formula k):



20 and wherein each of R^1 , R^2 , R^5 , R^6 , R^7 , R^8 , R^{10} , and R^{11} is independently selected from the group consisting of hydrogen, optionally substituted (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocyclyl.

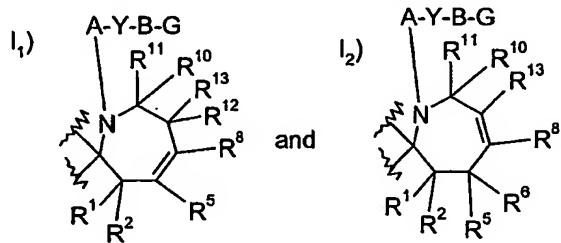
In another embodiment of the invention, the heterocyclic ring X has the formula k), as defined in the aforesaid paragraph, wherein in the heterocyclic ring X the dashed line is a double bond.

5 In another preferred embodiment of the invention, the heterocyclic ring X has the formula I):



and wherein each of R¹, R², R⁵, R⁶, R⁷, R⁸, R¹⁰, R¹¹, R¹² and R¹³ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

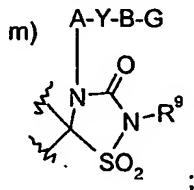
10 In another embodiment of the invention, the heterocyclic ring X has the formula I), wherein in the heterocyclic ring X the dashed line is a double bond, such that the heterocyclic ring X of formula I is selected from the group consisting of:



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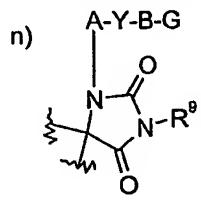
and wherein each of R¹, R², R⁵, R⁶, R⁷, R⁸, R¹⁰, R¹¹, R¹² and R¹³ is independently selected from the group consisting of hydrogen, optionally substituted (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₃-C₈)cycloalkyl and optionally substituted (C₁-C₁₀)heterocyclyl.

20 In another embodiment of the invention, the heterocyclic ring X has the formula m):



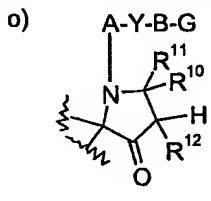
and wherein R^9 is selected from hydrogen, optionally substituted (C_1 - C_4)alkyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocycl; preferably R^9 is selected from hydrogen and (C_1 - C_4)alkyl, such as methyl.

5 In another embodiment of the invention, the heterocyclic ring X has the formula n):



and wherein R^9 is selected from hydrogen, optionally substituted (C_1 - C_4)alkyl, optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocycl; preferably R^9 is selected from hydrogen and (C_1 - C_4)alkyl, such as methyl.

10 In another embodiment of the invention, the heterocyclic ring X has the formula o):



and wherein each of R^{10} , R^{11} , and R^{12} is independently selected from the group consisting of hydrogen, optionally substituted (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, 15 optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocycl.

In each of the above embodiments of the invention, no more than a total of two of the R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} in any one (C_1 - C_{10})heterocycl preferably one ring X [i.e., ring a) to o)] are optionally substituted (C_6 - C_{10})aryl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_3 - C_8)cycloalkyl and optionally substituted (C_1 - C_{10})heterocycl.

In a preferred embodiment of each of the above embodiments of the invention, each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} is selected from hydrogen and (C_1 - C_4)alkyl, such as methyl.

25 In another preferred embodiment of each of the above embodiments of the invention, one or two of R^1 , R^2 , R^3 , R^4 , R^{10} , R^{11} , R^{12} and R^{13} is a group other than hydrogen.

In a more preferred embodiment of each of the above embodiments of the invention, each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} is hydrogen.

In another embodiment of each of the above embodiments of the invention, one or two of R⁵, R⁶, R⁷ and R⁸ is a group other than hydrogen.

In another embodiment of each of the above embodiments of the invention, R⁹ is selected from hydrogen, (C₁-C₄)alkyl, (C₆-C₁₀)aryl, (C₁-C₁₀)heteroaryl, (C₃-C₈)cycloalkyl and (C₁-C₁₀)heterocyclyl.

In another embodiment of each of the above embodiments of the invention, R⁹ is selected from hydrogen and (C₁-C₄)alkyl, such as methyl.

In each of the above embodiments of the invention, A is (C₁-C₁₀)heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably A is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl; more preferably A is pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; most preferably A is pyridinyl. Within each of the aforesaid embodiments, Y is selected from the group consisting of a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is -O-, -OCH₂- or -CH₂O-; more preferably Y is -O-.

In another embodiment of each of the above embodiments of the invention, A is (C₆-C₁₀)aryl, such as phenyl or naphthyl, wherein said (C₆-C₁₀)aryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably A is phenyl. Within each of the aforesaid embodiments, Y is selected from the group consisting of a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- and -CH₂O-; preferably Y is -O-, -OCH₂- or -CH₂O-; more preferably Y is -O-.

In another embodiment of the invention, A is substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy.

In another embodiment of the invention, B is a monocyclic saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom selected from the group

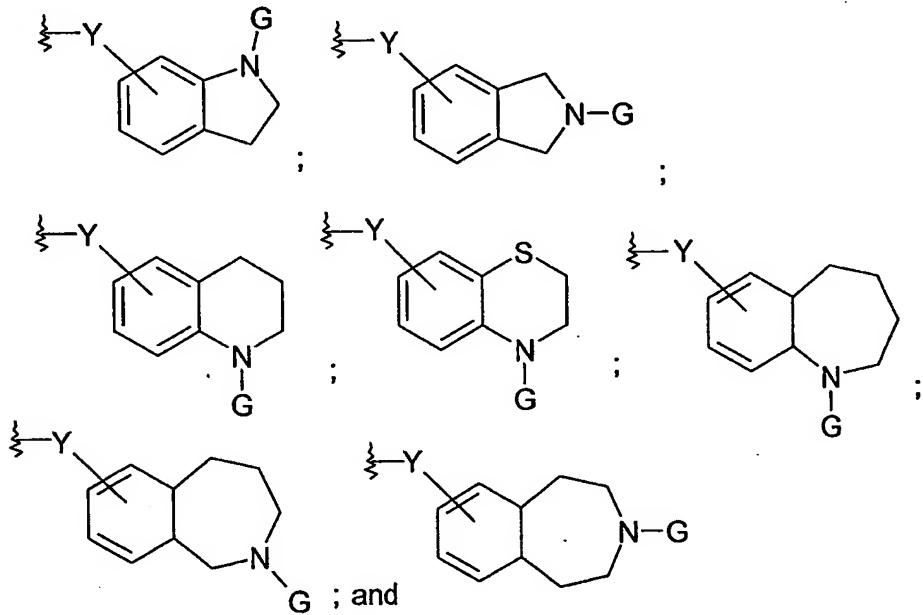
consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl.

In another embodiment of the invention, B is a monocyclic saturated (5- to 7-membered)-heterocyclic ring containing at least one ring nitrogen atom fused to an aromatic six membered ring, such as indolinyl or isoindolinyl.

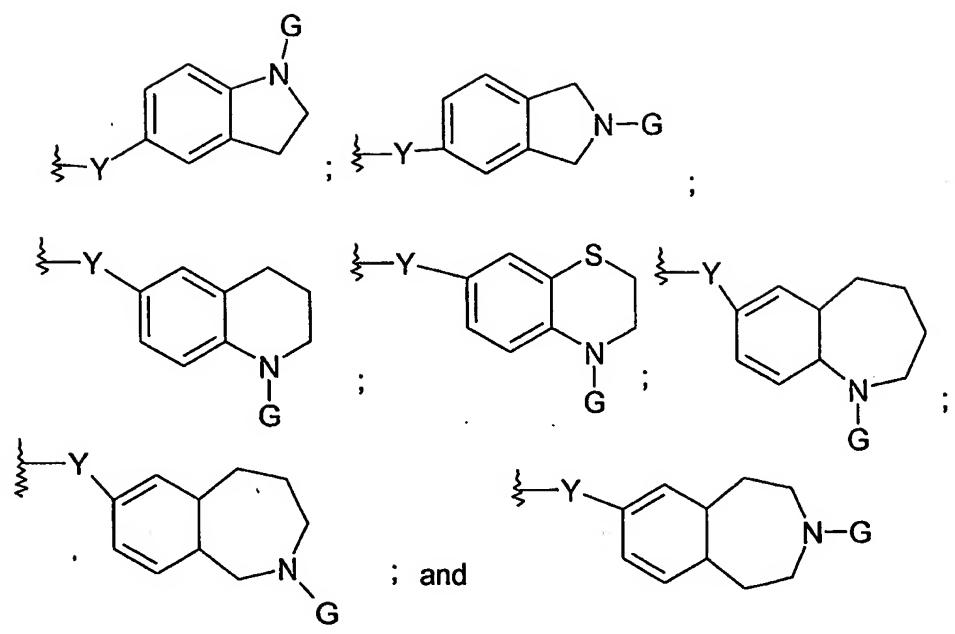
In another embodiment of the invention, Y is a bond, -O-, -S-, -CH₂-, >SO₂, -OCH₂- or -CH₂O-.

In another embodiment of the invention, Y is -O-, -OCH₂- or -CH₂O-; preferably Y is -O-.

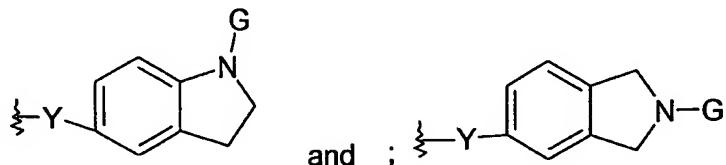
In another embodiment of the invention, the group -Y-B-G has the formulae selected from the group consisting of



preferably selected from the group consisting of



more preferably selected from the group consisting of



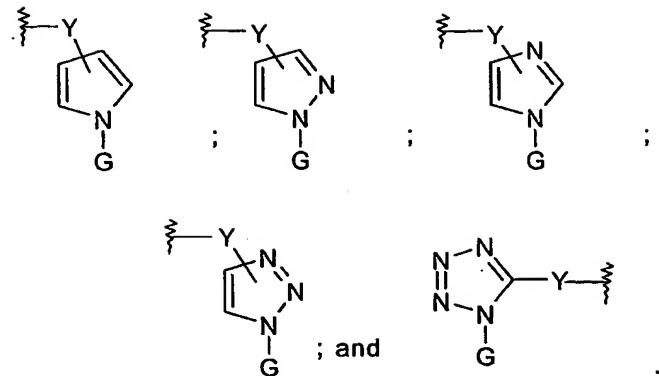
In another embodiment of the invention, B is a monocyclic partially saturated (5- to 7-membered)-ring containing at least one nitrogen atom, such as 2-pyrrolinyl, 3-pyrrolinyl, imidazolyl, 2-imidazolinyl, or 2-pyrazolinyl.

In another embodiment of the invention, B is a partially saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring, such as 3H-indolyl.

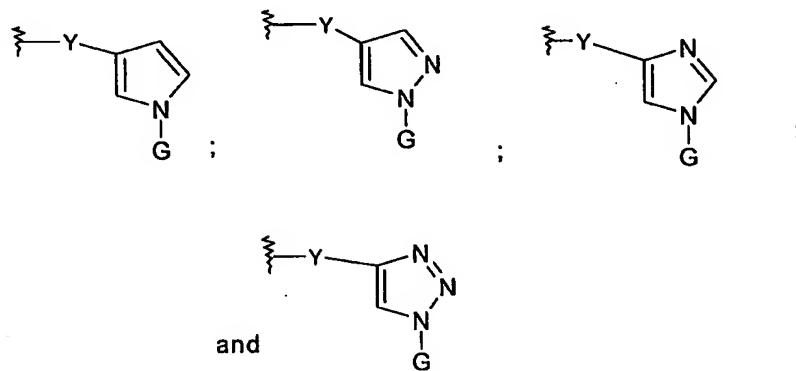
10 In another embodiment of the invention, B is a monocyclic aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom, such as tetrazolyl, pyrrolyl, imidazolyl, pyrazolyl, or triazolyl.

In another embodiment of the invention, the group -Y-B-G has the formulae selected from the group consisting of

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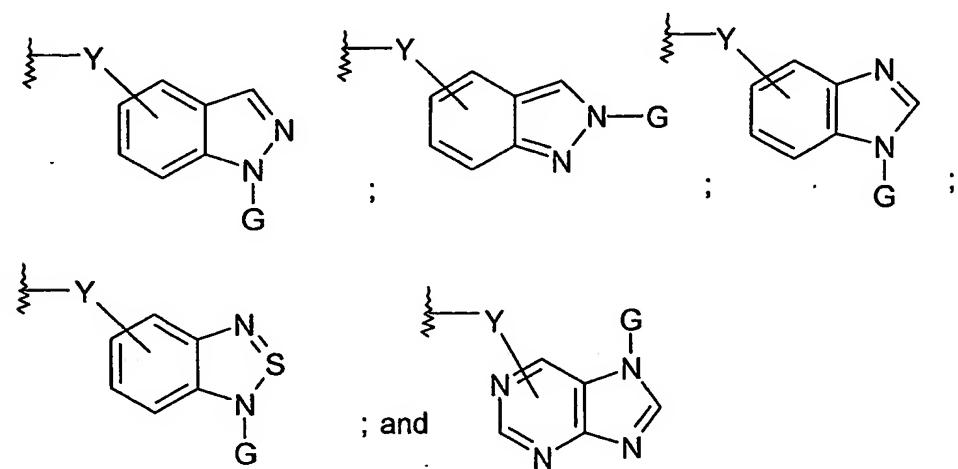


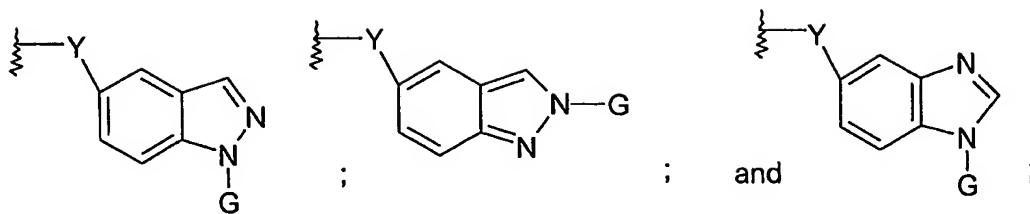
preferably selected from the group consisting of



and

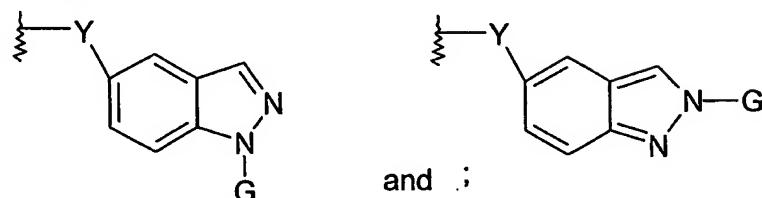
5 In another embodiment of the invention, B is an aromatic (5- to 6-membered)-ring containing at least one nitrogen atom fused to an aromatic six membered ring, such as indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, and purinyl; wherein the group -Y-B-G has the formulae selected from the group consisting of





;

more preferably selected from the group consisting of



5 In another embodiment of the invention, B is substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₃-C₈)cycloalkyloxy, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl, (C₁-C₁₀)heteroaryl and (C₁-C₁₀)heterocyclyl; preferably selected from F, Cl, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy.

10 In another embodiment of the invention, both A and B are substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably selected from the group consisting of F, Cl, CN, methyl, and methoxy.

15 In another preferred embodiment of the invention, either A or B is not substituted by any optional substituents.

 In another preferred embodiment of the invention, both A and B are not substituted by any optional substituents.

20 In another embodiment of the invention, G is (C₁-C₆)alkyl; wherein said G (C₁-C₆)alkyl may be optionally substituted on any of the carbon atoms capable of supporting an additional substituent by one to three substituents per (C₁-C₆)alkyl independently selected from F, Cl, Br, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; preferably selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; more preferably selected from F, Cl, CN, OH, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, and (C₃-C₈)cycloalkyloxy; most preferably selected from F, CN, OH, perfluoromethyl, methoxy, ethoxy, propoxy, cyclopentyloxy, and cyclohexyloxy;

In another embodiment of the invention, G is (C₃-C₈)cycloalkyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein said (C₃-C₈)cycloalkyl may also optionally be substituted by oxo.

In another embodiment of the invention, G is (C₆-C₁₀)aryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; preferably G is phenyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, and (C₃-C₈)cycloalkyloxy; more preferably G is phenyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one substituent per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another embodiment of the invention, G is unsubstituted (C₆-C₁₀)aryl; preferably G is unsubstituted phenyl.

In another embodiment of the invention, G is (C₁-C₁₀)heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinoliny, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably G is (C₁-C₁₀)heteroaryl selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and pyrazolyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; more preferably G is (C₁-C₁₀)heteroaryl selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl,

Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy; most preferably G is pyridinyl or pyridazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, 5 methoxymethyl, methoxyethyl, and cyclopentyloxy.

In another embodiment of the invention, G is unsubstituted (C₁-C₁₀)heteroaryl selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, fuopyridinyl, furyl, imidazolyl, indazolyl, 10 indoliny, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; preferably G is unsubstituted pyridinyl, pyridazinyl, or pyrazinyl.

15 In another embodiment of the invention, G is (C₁-C₁₀)heterocyclyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, 20 (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein said (C₁-C₁₀)heterocyclyl may also optionally be substituted by oxo.

In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; and wherein each of R¹⁶ or R¹⁷ is independently hydrogen, methyl, ethyl, propyl, or isopropyl.

25 In another embodiment of the invention, G is R¹⁵-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; and wherein R¹⁶ and R¹⁷ are taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, and cyclohexenyl.

30 In another embodiment of the invention, G is (C₃-C₈)cycloalkyl-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; wherein said (C₃-C₈)cycloalkyl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; wherein said (C₃-C₈)cycloalkyl may also optionally be substituted by oxo; and wherein each of R¹⁶ and R¹⁷ is 35 independently hydrogen.

In another embodiment of the invention, G is (C₆-C₁₀)aryl-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; wherein said (C₆-C₁₀)aryl is optionally

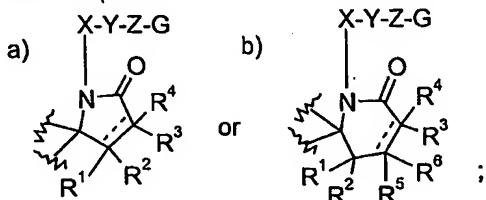
substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein each of R¹⁶ and R¹⁷ is independently hydrogen.

In another embodiment of the invention, G is (C₁-C₁₀)heteroaryl-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; wherein said (C₁-C₁₀)heteroaryl is selected from the group consisting of benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, 10 benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl; wherein said (C₁-C₁₀)heteroaryl is optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; preferably said (C₁-C₁₀)heteroaryl is selected from the group consisting of imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl and 15 pyrazolyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy and (C₃-C₈)cycloalkyloxy; more preferably said (C₁-C₁₀)heteroaryl is selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl optionally substituted on any of the ring carbon 20 atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy; most preferably said (C₁-C₁₀)heteroaryl is pyridinyl or pyridazinyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to two substituents per ring independently selected from F, Cl, Br, CN, OH, methyl, ethyl, isopropyl, methoxy, methoxymethyl, methoxyethyl, and cyclopentyloxy; and wherein each of R¹⁶ and R¹⁷ is independently hydrogen.

In another embodiment of the invention, G is (C₁-C₁₀)heterocycl-(CR¹⁶R¹⁷)_p-; wherein p is an integer from one to four, preferably from one to two; wherein said (C₁-C₁₀)heterocycl is optionally substituted on any of the ring carbon atoms capable of supporting an additional 35 substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein said

(C₁-C₁₀)heterocycl₁ may also optionally be substituted by oxo; and wherein each of R¹⁸ and R¹⁷ is independently hydrogen.

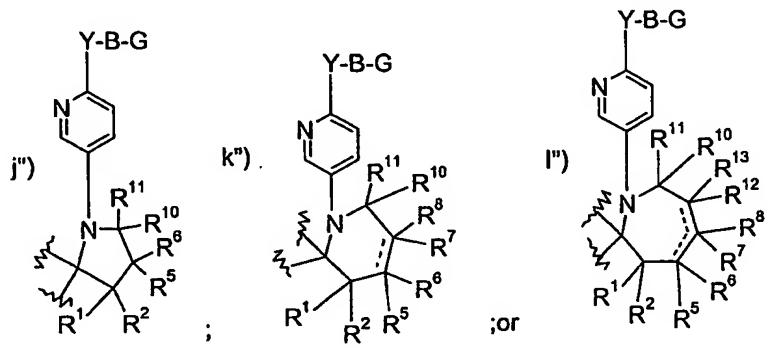
In another preferred embodiment of the invention, the heterocyclic ring X has the formula i), k) or l), as defined above; wherein A is (C₁-C₁₀)heteroaryl selected from the group



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consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably A is pyridinyl; most preferably A is pyridin-2-yl or pyridin-3-yl; and Y is selected from the group consisting of a bond, -O-, -S-, -CH₂, >SO₂, -OCH₂- and -CH₂O-; more preferably Y is -O-, -OCH₂- or -CH₂O-; most preferably Y is -O-.

10 In another preferred embodiment of the invention, the heterocyclic ring X has the formula j), k), or l), as defined above; wherein A is (C₁-C₁₀)heteroaryl selected from the group consisting of pyrazinyl, pyridazinyl, pyridyl and pyrimidinyl; more preferably A is pyridinyl; most preferably A is pyridin-2-yl or pyridin-3-yl; most preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formulae:



15

wherein Y is a bond, $-O-$, $-S-$, $-CH_2-$, $>SO_2-$, $-OCH_2-$ or $-CH_2O-$; preferably Y is $-O-$, $-OCH_2-$ or $-CH_2O-$; more preferably Y is $-O-$.

In another embodiment of the invention, the heterocyclic ring X the formula j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula j"), k") or l") as defined above; Y is -O-; B is a monocyclic partially saturated (5- to 7-membered)-ring containing at least one nitrogen atom; G is (C₁-C₆)alkyl, preferably propyl or isopropyl, optionally substituted on any of the carbon atoms capable of supporting an additional substituent by one to three F, Cl, Br, CN, OH, methoxy, cyclopentyloxy and cyclohexyloxy.

25 In another embodiment of the invention, the heterocyclic ring X is the formula j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and

the group -Y-B-G has the formula j"), k") or l"), as defined above; Y is -O-; B is a monocyclic aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom; G is (C₁-C₁₀)heteroaryl, preferably pyridinyl, pyrazinyl or pyridazinyl.

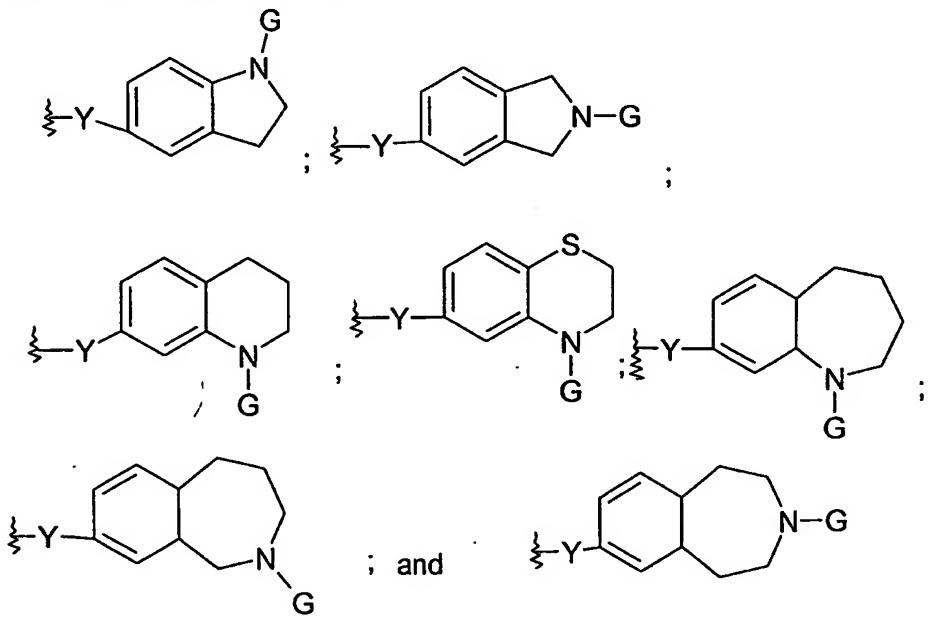
In another embodiment of the invention, the heterocyclic ring X the formula j), k), or l),

5 as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula j"), k") or l"), as defined above; Y is -O-; B is an aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring, preferably 1H-indazolyl, 2H-indazolyl, or benzimidazolyl; G is (C₁-C₁₀)heteroaryl, preferably pyridinyl, pyrazinyl or pyridazinyl.

10 In another embodiment of the invention, the heterocyclic ring X the formula j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula j"), k") or l"), as defined above; Y is -O-; B is an aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring, preferably 1H-indazolyl, 2H-indazolyl, or benzimidazolyl; G is (C₁-C₁₀)heteroaryl-(CR¹⁶R¹⁷)p-; wherein p is one and each of R¹⁶ and R¹⁷ are independently hydrogen.

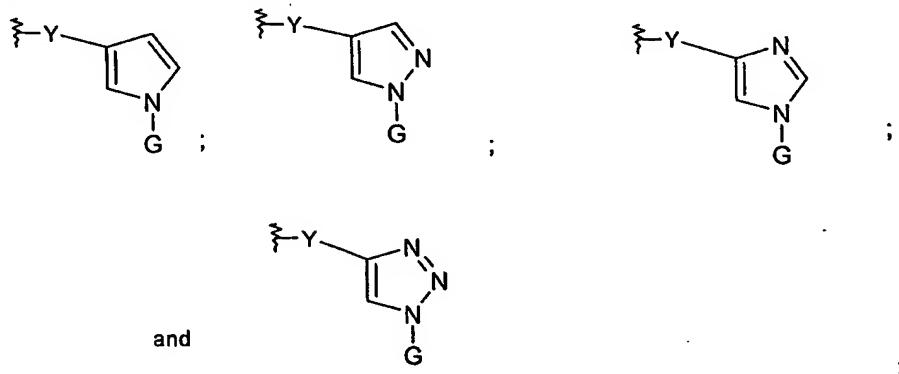
15 In another embodiment of the invention, the heterocyclic ring X the formula j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula j"), k") or l"), as defined above; Y is -O-; the group -Y-B-G

20 has the formulae selected from the group consisting of



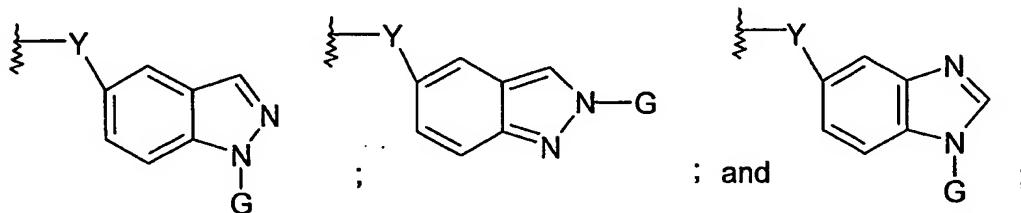
G is (C₁-C₁₀)heteroaryl, preferably pyridinyl, pyrazinyl or pyridazinyl.

In another embodiment of the invention, the heterocyclic ring X the formula j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula j"), k") or l"), as defined above; Y is -O-; the group -Y-B-G has the formulae selected from the group consisting of



G is (C₁-C₁₀)heteroaryl, preferably pyridinyl, pyrazinyl or pyridazinyl.

In another preferred embodiment of the invention, the heterocyclic ring X has the formula (j), k), or l), as defined above; A is pyridinyl, preferably wherein the pyridinyl together with the X ring and the group -Y-B-G has the formula (j"), k") or l"), as defined above; Y is -O-; the group -Y-B-G has the formulae selected from the group consisting of



G is (C₁-C₁₀)heteroaryl, preferably pyridinyl, pyrazinyl or pyridazinyl.

Other compounds of the invention are selected from the group consisting of:

1-[6-(1-Isopropyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Isopropyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione:

4-{5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-2-yl}-benzonitrile

20 1-[6-[2-(2-Hydroxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(2-Ethoxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Fluoro-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-[1-(4-Fluoro-phenyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-3-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-[2-(4-Fluoro-phenyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-3-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-[2-(4-Fluoro-phenyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-[1-(4-Fluoro-phenyl)-1H-benzoimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl]-nicotinonitrile;

1-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3-dihydro-indol-1-yl]-nicotinonitrile;

30 1-[6-(2-Pyridin-3-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

6-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-2H-quinolin-1-yl]-nicotinonitrile;

1-[6-(1-Pyridin-4-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(1-Pyridin-3-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

6-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-1H-isoquinolin-2-yl]-nicotinonitrile;

40 6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-1,3-dihydro-isoindol-2-yl]-nicotinonitrile;

6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-1-yl]-nicotinonitrile;

6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-2-yl]-nicotinonitrile;

5 1-[6-(2-Pyridin-4-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-4-yl-1H-benzoimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(2-Pyridin-4-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-3-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(1-Pyridin-4-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-3-yl-1H-benzoimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-(1-Pyridin-4-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-4-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-(1-Pyridin-3-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-p-Tolyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-(2-p-Tolyl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Chloro-phenyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(2-Pyridin-2-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-2-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(3-Methoxy-propyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridazin-3-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-(1-Isopropyl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(1-Isopropyl-1H-benzoimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(2-Isopropyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-(2-Isopropyl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-(2-Pyridazin-3-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-(2-Isopropyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(2-Pyridazin-3-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(3-Methoxy-propyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(3-Methoxy-propyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Methoxy-phenyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(3-Methoxy-propyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridazin-3-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-p-Tolyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-2-yl]-benzonitrile;

1-[6-[1-(4-Methoxy-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-[2-(4-Chloro-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

4-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-1H-isoquinolin-2-yl]-benzonitrile;

10 4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3-dihydro-indol-1-yl]-benzonitrile;

1-[6-[1-(4-Methoxy-phenyl)-1H-benzoimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 4-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-2H-quinolin-1-yl]-benzonitrile;

1-[6-[1-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 4-[7-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl]-benzonitrile;

4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-1,3-dihydro-isoindol-2-yl]-benzonitrile;

1-[6-[1-(4-Chloro-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-(1-p-Tolyl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzoimidazol-1-yl]-benzonitrile;

1-[6-[1-(3-Methoxy-propyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-[1-(4-Chloro-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-p-Tolyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-[2-(4-Methoxy-phenyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridazin-3-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-1-yl]-benzonitrile;

5 1-[6-(1-p-Tolyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Methoxy-phenyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(1-Pyridazin-3-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridazin-3-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(1-Pyridazin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-(1-Pyridin-2-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-[1-(4-Methoxy-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Chloro-phenyl)-1H-benzimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-[1-(3-Methoxy-propyl)-1H-benzimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(3-Methoxy-propyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-[1-(4-Chloro-phenyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-p-Tolyl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione; and

1-[6-(1-p-Tolyl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

or the pharmaceutically acceptable salts thereof.

The present invention also relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, 5 cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other diseases characterized by metalloproteinase activity in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically 10 acceptable carrier.

The present invention also relates to a pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of formula I effective in such treatment and a pharmaceutically acceptable carrier.

15 The present invention also relates to a method for the inhibition of matrix metalloproteinases in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I.

The present invention also relates to a method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy 20 disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers and other diseases characterized by matrix metalloproteinase activity in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

The present invention also relates to a method for the inhibition of matrix metalloproteinases or other metalloproteinases involved in matrix degradation, in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

30 The present inventors have also discovered that it is possible to identify inhibitors of formula I with differential metalloprotease activity (preferably MMP-13 inhibitory activity). One group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1. The compounds of the invention also possess selectivity over a related group of enzymes known as reproxysins, such as TACE 35 and aggrecanase. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and MMP-14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1 and 12.

Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 12 and 14. Another group of preferred inhibitors of formula I the inventors have been able to identify include those which selectively inhibit MMP-13 preferentially over MMP-1, 2, 3, 7, 9 and 14. Most preferred 5 compounds of the invention selectively inhibit MMP-13 preferentially over any two or more of MMP-1, 2, 3, 7, 9, 12 and 14 and mammalian reproxlysins.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically 10 effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione exhibits: i) a ratio of MMP-1 IC₅₀ / MMP-13 IC₅₀ of about 50, and ii) a ratio of MMP-14 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein said MMP-1 IC₅₀ is measured by a recombinant MMP-1 assay; wherein each of said MMP-13 IC₅₀ is measured by a recombinant 15 MMP-14 assay; and wherein said MMP-14 IC₅₀ is measured by a recombinant MMP-14 assay.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione additionally exhibits iii) a ratio of MMP-12 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein said MMP-12 IC₅₀ is measured by a recombinant MMP-12 assay; and wherein said MMP-13 IC₅₀ is measured by a recombinant MMP-13 assay.

The present invention also relates to a method for treating a medical condition of the type that is characterized by the destruction of articular cartilage in a mammalian subject, 25 which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably substituted pyrimidine-2,4,6-trione additionally exhibits iv) a ratio of MMP-2 IC₅₀ / MMP-13 IC₅₀ of about 50, and v) a ratio of MMP-3 IC₅₀ / MMP-13 IC₅₀ of about 50; vi) a ratio of MMP-7 IC₅₀ / MMP-13 IC₅₀ of about 50, and vii) a ratio of MMP-9 IC₅₀ / MMP-13 IC₅₀ of about 50; wherein 30 said MMP-2 IC₅₀ is measured by a recombinant MMP-2 assay; wherein said MMP-3 IC₅₀ is measured by a recombinant MMP-3 assay; wherein said MMP-7 IC₅₀ is measured by a recombinant MMP-7 assay; wherein said MMP-9 IC₅₀ is measured by a recombinant MMP-9 assay; and each of said MMP-13 IC₅₀ is measured by a recombinant MMP-13 assay.

The present invention also relates to a method for treating a medical condition of the 35 type that is characterized by the destruction of articular cartilage in a mammalian subject, which method comprises administering to the subject having said condition a therapeutically effective amount of a suitably substituted pyrimidine-2,4,6-trione, wherein said suitably

substituted pyrimidine-2,4,6-trione exhibits an MMP-13 IC₅₀ of less than about 100nM, preferably of less than about 50 nM; more preferably of less than about 20 nM.

5 The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

"Connective tissue disorders" as used herein refers to disorders such as degenerative cartilage loss following traumatic joint injury, osteoarthritis, osteoporosis, Paget's disease, loosening of artificial joint implants, periodontal disease and gingivitis.

10 "Destruction of articular cartilage" as used herein refers to connective tissue disorders resulting in articular cartilage destruction, preferably joint injury, reactive arthritis, acute pyrophosphate arthritis (pseudogout), psoriatic arthritis, or juvenile rheumatoid arthritis, more preferably osteoarthritis.

15 "Inflammatory disorders" as used herein refers to disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, chondrocalcinosis, gout, inflammatory bowel disease, ulcerative colitis, Crohn's disease, fibromyalgia, and cachexia.

20 "Immunology/allergy disorders" as used herein refers to disorders such as organ transplant toxicity, allergic reactions, allergic contact hypersensitivity, autoimmune disorders such as those disorders associated with granulomatous inflammation/tissue remodeling (such as asthma), immunosuppression and sarcoid.

"Infectious diseases," including those mediated by viruses, bacteria, fungi or mycobacterial infection, as used herein refers to disorders such as septic arthritis, AIDS, fever; Prion diseases, myasthenia gravis, Malaria, sepsis, hemodynamic shock and septic shock.

25 "Respiratory diseases" as used herein refers to disorders such as chronic obstructive pulmonary disease (including emphysema), acute respiratory distress syndrome, asthma, hyperoxic alveolar injury and idiopathic pulmonary fibrosis and other fibrotic lung diseases.

30 "Cardiovascular diseases" as used herein refers to disorders such as atherosclerosis including atherosclerotic plaque rupture; aortic aneurysm including abdominal aortic aneurysm and brain aortic aneurysm; congestive heart failure; myocardial and cerebral infarction; stroke; cerebral ischemia; coagulation and acute phase response; left ventricular dilation; post ischemic reperfusion injury; angiofibromas; hemangiomas; and restenosis.

35 "Eye diseases" as used herein refers to disorders such as aberrant angiogenesis, ocular angiogenesis, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, neovascular glaucoma, corneal ulceration, corneal scarring, macular degeneration (including "Age Related Macular Degeneration (ARMD) including both wet and dry forms), proliferative vitreoretinopathy and retinopathy of prematurity.

"Metabolic diseases" as used herein refers to disorders such as diabetes (including non-insulin dependent diabetes mellitus, diabetic retinopathy, insulin resistance, diabetic ulceration).

"Central Nervous System" (CNS) disorders as used herein refers to disorders such as

5 head trauma, spinal cord injury, Inflammatory diseases of the central nervous system, neuro-degenerative disorders (acute and chronic), Alzheimer's disease, demyelinating diseases of the nervous system, Huntington's disease, Parkinson's disease, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, migraine, depression and anorexia.

10 "Liver/Kidney diseases" as used herein refers to disorders such as nephrotic syndromes such as glomerulonephritis and glomerular disease of the kidney, proteinuria, cirrhosis of the liver and interstitial nephritis.

15 "Reproductive Health disorders" as used herein refers to disorders such as endometriosis, contraception (male/female), dysmenorrhea, dysfunctional uterine bleeding, premature rupture of fetal membranes and abortifacient.

"Gastric disorders" as used herein refers to disorders such as colonic anastomosis and gastric ulcers.

20 "Skin disorders" as used herein refers to disorders such as skin aging, pressure sores, psoriasis, eczema, dermatitis, radiation damage, tissue ulceration, decubital ulcers, epidermolysis bullosa, abnormal wound healing (topical and oral formulations), burns and scleritis.

25 "Cancers" as used herein refers to disorders such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostate cancer, tumor invasion, tumor growth tumor metastasis, cancers of the oral cavity and pharynx (lip, tongue, mouth, pharynx), esophagus, stomach, small intestine, large intestine, rectum, liver and biliary passages, pancreas, larynx, lung, bone, connective tissue, skin, cervix uteri, corpus endometrium, ovary, testis, bladder, kidney and other urinary tissues, eye brain and central nervous system, thyroid and other endocrine gland, Hodgkin's disease, non-Hodgkin's lymphomas, multiple myeloma and hematopoietic malignancies including leukemias and lymphomas including lymphocytic, 30 granulocytic and monocytic.

35 The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, -O-, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned

Isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly 5 preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled 10 compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

This invention also encompasses pharmaceutical compositions containing prodrugs of 15 compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of matrix metalloproteinases or the inhibition of mammalian reprodysin comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy, sulfonamide or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues 20 which are covalently joined through peptide bonds to free amido, amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine 25 sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters, which are covalently, bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include dimers of compounds of formula I.

One of ordinary skill in the art will appreciate that the compounds of the invention are 30 useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies 35 (such as infliximab, D2E7 and CDP-870) and TNF receptor immunoglobulin molecules (such as etanercept), ICE inhibitors, MEKK1 inhibitors, COX-2 inhibitors such as celecoxib, rofecoxib, valdecoxib and etoricoxib; low dose methotrexate, lefunimide, steroids,

glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release inhibitors, IL-1 receptor antagonists such as Kineret®, CCR-1 antagonists, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, paracoxib, etoricoxib and rofecoxib, analgesics, steroids, glucosamines, chondrosamines/ sulfates, gabapentin, A-agonists, IL-1 process and release inhibitors, CCR-1 antagonists, LTD-4, LTB-4 and 5-LO inhibitors, p38 kinase inhibitors and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

15 The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, paclitaxel, docetaxel and alkaloids, such as vincristine and antimetabolites such as methotrexate.

20 The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers (such as amlodipine and nifedipine), lipid lowering agents such as statins (such as lovastatin, atorvastatin, pravastatin and simvastatin), adrenergics such as doxazosin and terazosin; fibrates, beta-blockers, ACE inhibitors (such as captopril, lisinopril, fosinopril, enalapril and quinapril), Angiotensin-2 receptor antagonists such as losartan and irbesartan; nitrates, CCB's, diuretics such as 25 digitalis and platelet aggregation inhibitors. The compounds of the present invention may also be used in combination with plaque rupture preventative agents such as statins, zithromax, NSAIDs including aspirin, heparin, warfarin, abciximab, TPA and platelet Inhibitors. The compounds of the present invention may also be used in combination with stroke treatment agents such as NIF, NHEI's and CCR1 antagonists.

30 The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, carbadopa, L-dopa, dopamine receptor agonists such as ropinirole, pergolide and pramipexole; MAOB inhibitors such as selegiline and rasagiline, catechol-O-methyltransferase inhibitors such as tolcapone, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, 35 Nicotine agonists, NK-1 inhibitors, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxitene, droloxitene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

The compounds of the present invention may also be used in combination with agents for the treatment of respiratory diseases such as PDE-IV inhibitors, steroidals such as fluticasone, triamcinolone, budesonide, budesonide and beclomethasone, anticholinergics such as ipratropium, sympathomimetics such as salmeterol, albuterol and Xopenex, decongestants such as fexofenadine, loratadine and cetirizine; leukotriene antagonists such as zafirlukast and montelukast; and mast cell stabilizers such as zileuton.

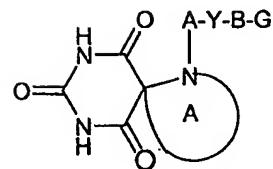
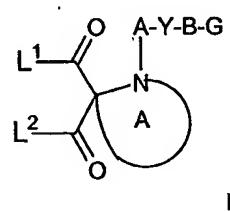
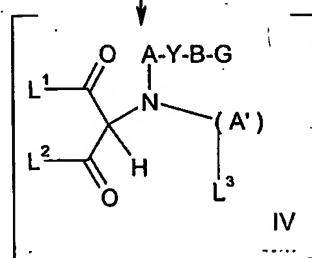
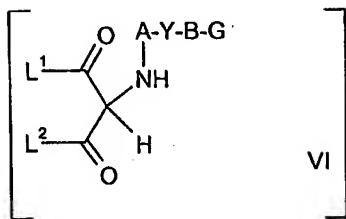
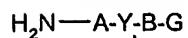
10. The compounds of the present invention may also be used in combination with agents for the treatment of skin disorders such as tretinoin, isotretinoin, steroids such as cortisone and mometasone, antibiotics such as tetracycline, antifungals such as clotrimazole, miconazole and fluconazole and PDE-IV inhibitors.

The compounds of the present invention may also be used in combination with agents for the treatment of diabetes such as insulin, including human or humanized insulin and inhaled insulin, aldose reductase inhibitors, sorbitol dehydrogenase inhibitors, antidiabetic agents such as biguanides such as metformin; glitazones, glycosidase inhibitors such as acarbose, sulfonylureas such as glimepiride and glipizide; and thiazolidinediones such as pioglitazone, rosiglitazone and troglitazone. Preferred combinations are useful for treating the side effects of diabetes such as retinopathy, nephropathy and neuropathy, preferably retinopathy.

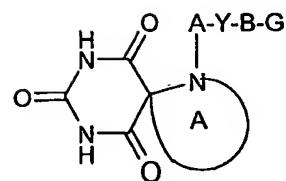
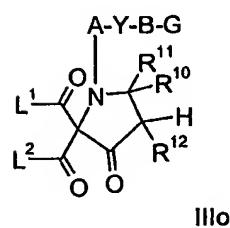
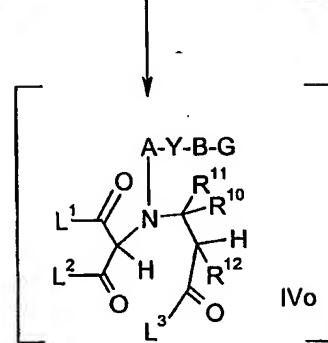
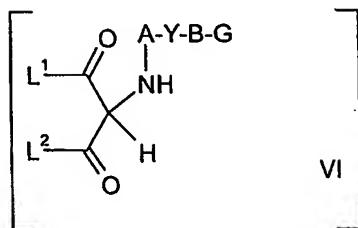
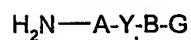
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated each of A, Y, B, G, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, and R¹⁷ in the reaction Schemes and the discussion that follows is defined as above.

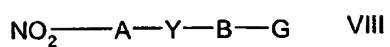
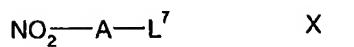
-37-

SCHEME 1

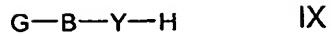
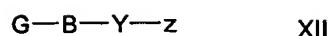
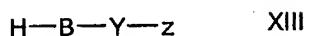
-38-

SCHEME 2

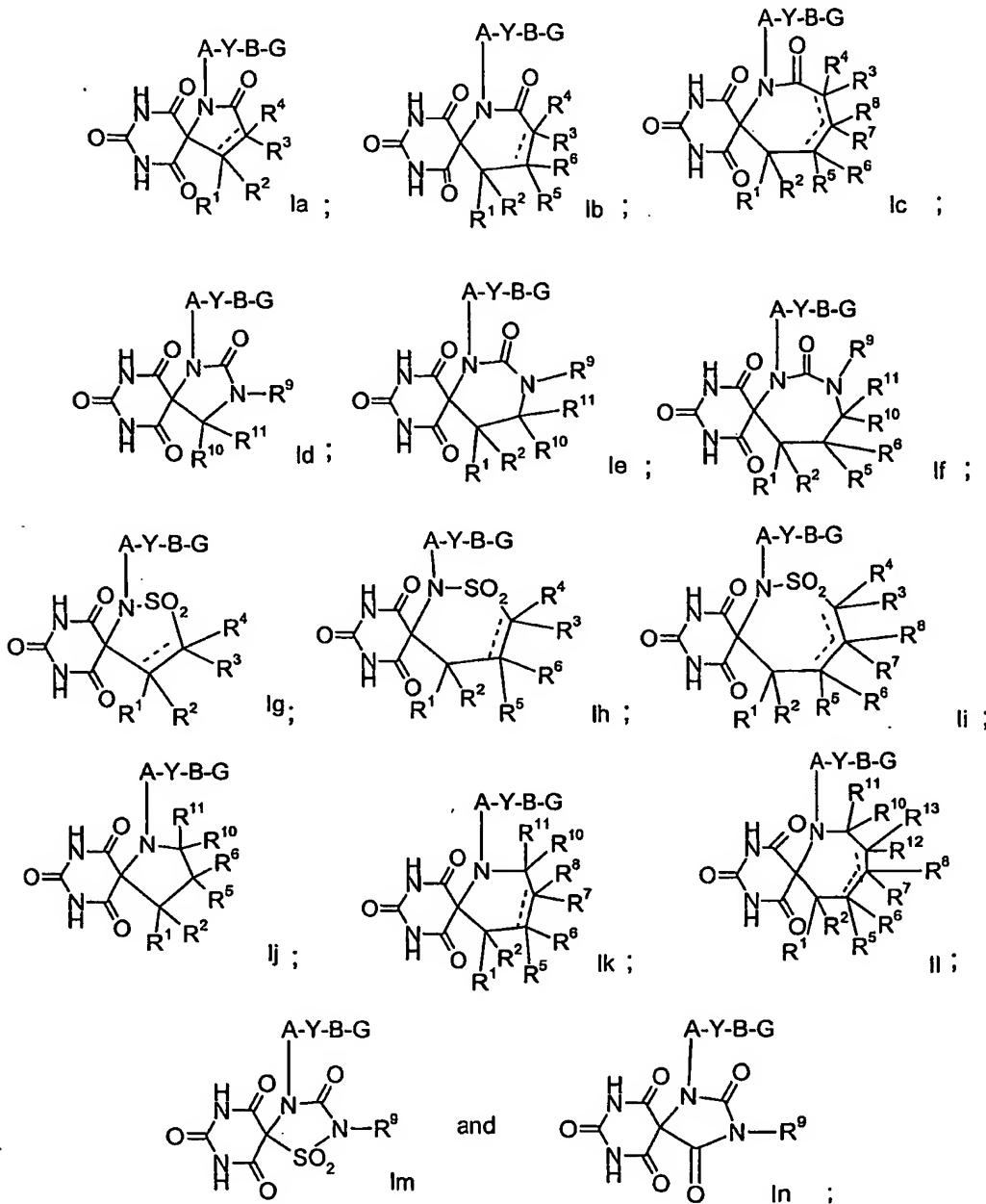
-39-

SCHEME 3

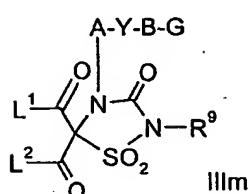
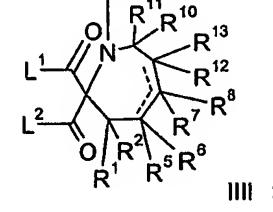
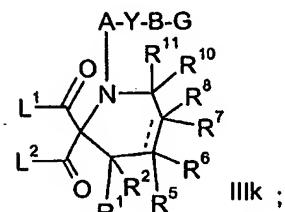
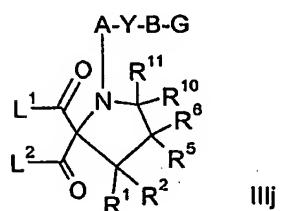
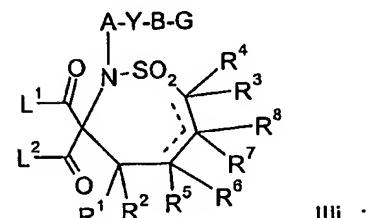
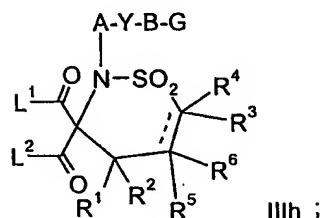
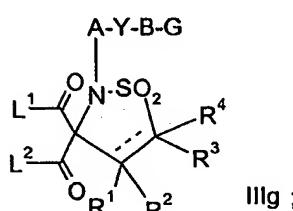
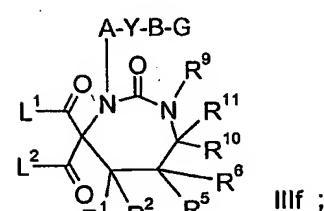
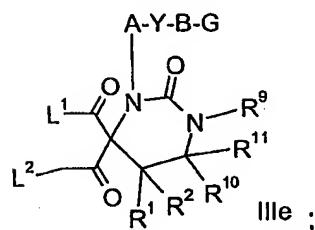
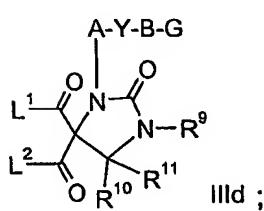
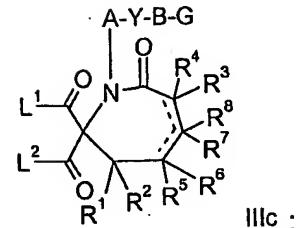
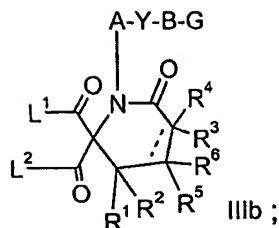
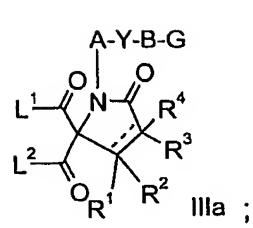
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SCHEME 4

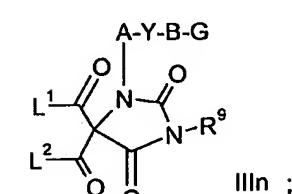
Scheme 1 refers to the preparation of compounds of the formula I. Referring to Scheme 1, compounds of formula I, wherein the heterocyclic ring X has the formulae a-n (i.e., a compound of the formulae Ia-In, respectively):



can be prepared by reacting a compound of the formulae IIIa-IIIi, respectively:



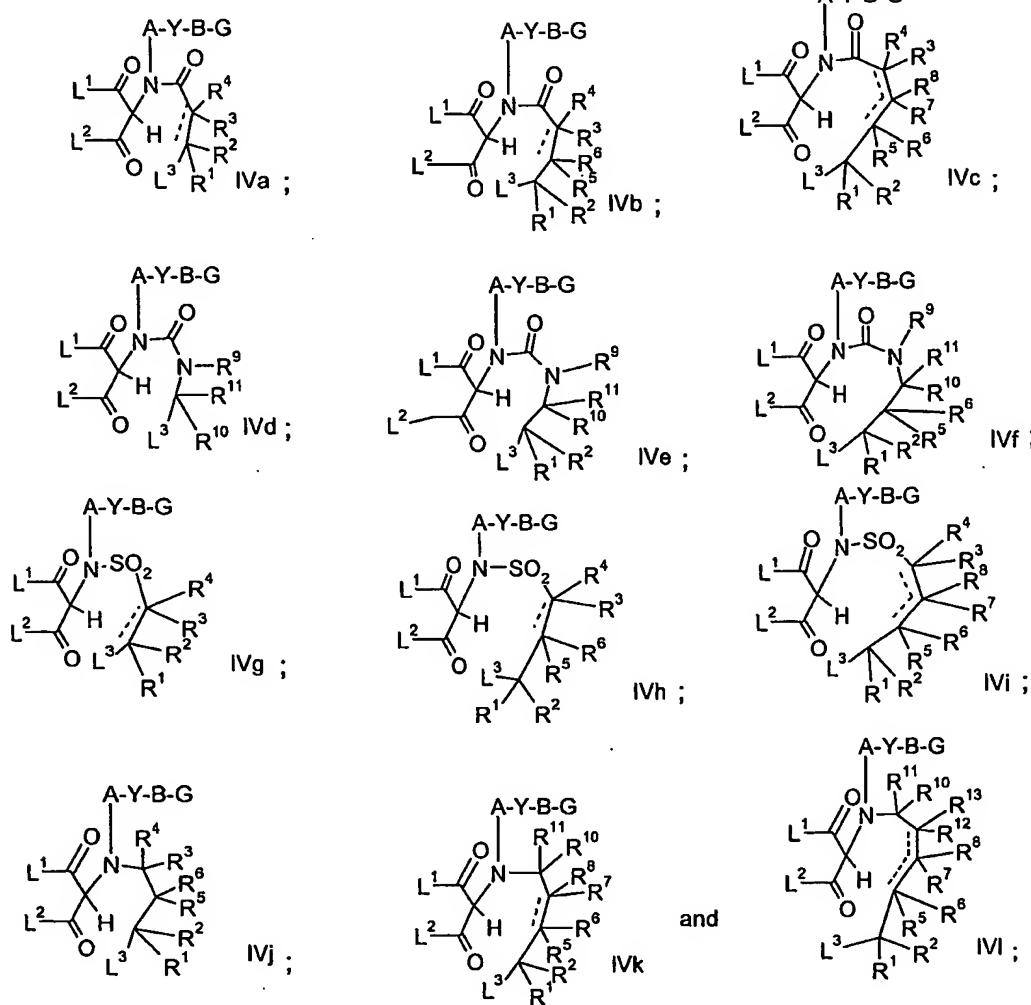
and



wherein L^1 and L^2 are leaving groups such as alkoxy, preferably methoxy, ethoxy or benzyloxy, more preferably methoxy or ethoxy, with a urea of formula II (i.e., $H_2N-(CO)-NH_2$) in the presence of a suitable base in a polar solvent. Suitable bases include alkoxide bases, such as sodium methoxide, sodium ethoxide, or potassium *tert*-butoxide, preferably sodium ethoxide; or hydride bases, such as sodium hydride. Suitable solvents include DMSO tetrahydrofuran, dimethylformamide (DMF), or alcohols (such as ethanol), preferably tetrahydrofuran or dimethylformamide (DMF). The aforesaid reaction is conducted at a temperature of about 5

0°C to about 90°C, preferably about 20°C to about 80°C, for a time period of about 5 minutes to about 8 hours.

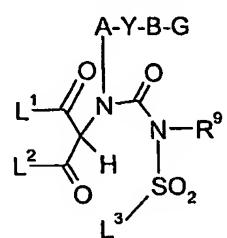
A compound of formulae IIIa-III, respectively, can be prepared by reacting a compound of formulae IVa-IVI, respectively:



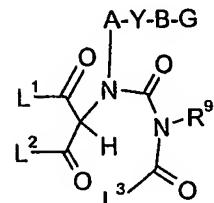
5

wherein L^1 and L^2 are leaving groups such as alkoxy, preferably methoxy, ethoxy or benzyloxy, more preferably methoxy or ethoxy and wherein L^3 is a suitable leaving group, such as halo, para-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs), preferably halo, such as bromo or iodo, with a suitable base in a polar solvent. Suitable bases include tertiary amines, such as 10 triethylamine. Other suitable bases include a strongly basic macro-reticular resin or gel type resin, such as Amberlyst 400® resin (hydroxide form). Suitable solvents include alcoholic solvents, preferably ethanol. The aforesaid reaction can be conducted at a temperature of about -10 °C to about 50 °C, preferably about 20 °C, for a period of about 6 to about 36 hours.

A compound of formulae IIIm-IIIn, respectively, can be prepared by reacting a compound of formulae IVm-IVn, respectively:



IVm



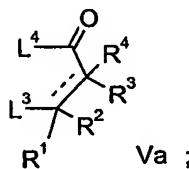
IVn

wherein L³ is a suitable leaving group, with a suitable base in a polar solvent according to methods analogous to the preparation of the compounds of formulae IIIa-IIIi in the foregoing paragraph. Suitable leaving groups of the formula L³ include halo, para-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs). Preferably L³ is halo, such as chloro. The aforesaid reaction can be conducted at a temperature of about 0°C to about 50°C, preferably about 20 °C, for a period of about 1 hour to about 4 hours. Suitable solvents include tetrahydrofuran, dimethylformamide and alcohol.

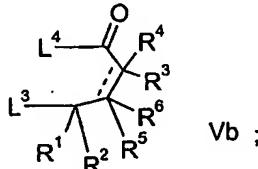
A compound of formulae IVa-IVi, respectively, can be prepared by reacting a compound of formula VI with a compound of general formula



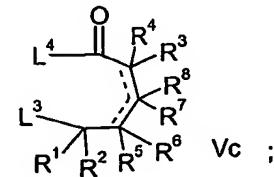
(i.e., a compound of formulae Va-Vi, respectively):



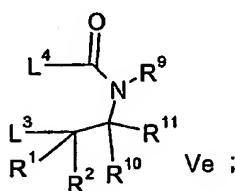
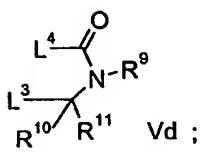
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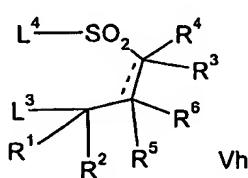
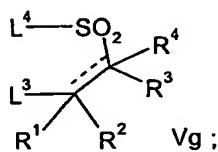
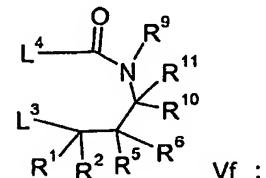
Vb ;



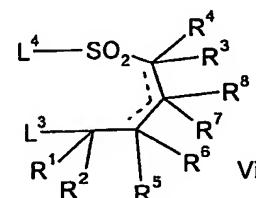
Vc ;



Ve ;



and



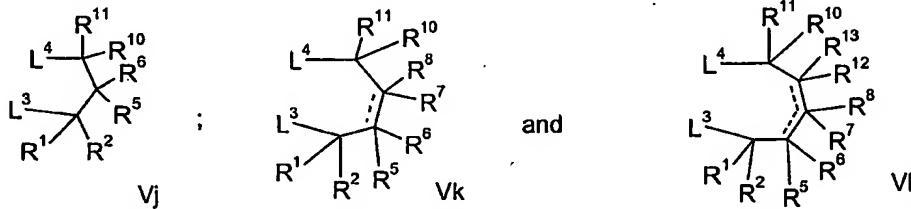
wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs), or methylsulfonyloxy (OMs). Preferably L^3 is halo, such as bromo, chloro or iodo. Preferably L^4 is chloro or fluoro. Optionally, the aforementioned reaction may be conducted in the presence of a tertiary amine base, such as *N,N*-dimethylaniline or pyridine, in the presence 5 of a suitable solvent, such as a hydrocarbon solvent (benzene or toluene), tetrahydrofuran or methylene chloride. The aforementioned reaction is conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 30 minutes to about 6 hours.

Preferably, the aforementioned reaction is conducted in an aromatic hydrocarbon 10 solvent, such as benzene or toluene, in the absence of the aforementioned base.

A compound of formulae IVj-IVl, respectively, can be prepared by reacting a compound of formula VI with a compound of formula:



(i.e., a compound of formulae Vj-Vl, respectively):

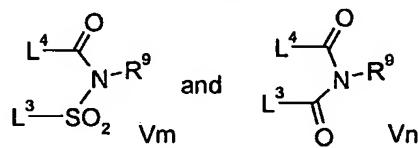


wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), according to the methods analogous to those described in the preparation of the compounds of formulae IVa-IVi in the foregoing paragraph. Preferably L^3 is chloro, bromo, or iodo. Preferably L^4 is chloro, bromo, or iodo. The aforesaid reaction can be 20 conducted at a temperature of about 0°C to about 50°C, preferably about 20°C, for a time period of about 30 minutes to about 12 hours. Preferably, the reaction is performed in the presence of a suitable base, such as sodium hydride or cesium carbonate.

Compounds of formulae IVm-IVn, respectively, can be prepared by reacting a compound of formula VI with a compound of formula



(i.e., a compound of formulas Vm-Vn, respectively):



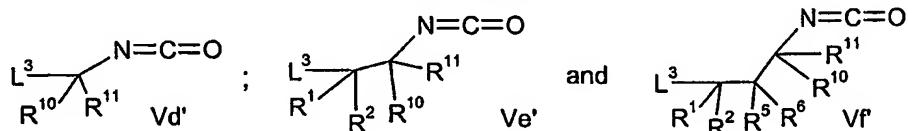
wherein each of L^3 and L^4 is a suitable leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs), according to the methods analogous to those described in the preparation of the compounds of formulae IVa-IVi in the foregoing paragraph. Preferably L^3 is 30

halo, such as chloro. Preferably L^4 is halo, such as chloro. The aforesaid reaction can be conducted at a temperature of about 0°C to about 80°C, preferably about 0°C to about 40°C, for a time period of about 30 minutes to about 8 hours.

Alternatively, compounds of formulae IVd, IVe and IVf, respectively, can be prepared by 5 reacting a compound of formula VI with a compound of formula



(i.e., a compound of formulae Vd', Ve' and Vf', respectively):

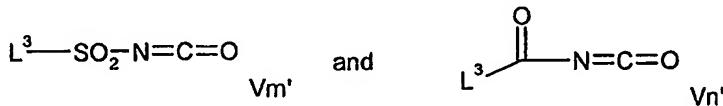


wherein L³ is preferably halo, most preferably chloro, bromo, or iodo. Optionally, the 10 aforementioned reaction can be conducted in the presence of a tertiary amine base in a suitable solvent. Suitable bases include *N,N*-dimethylaniline or pyridine. Suitable solvents include hydrocarbon solvent (benzene or toluene), tetrahydrofuran, or methylene chloride, preferably aromatic hydrocarbon solvent, such as benzene or toluene. The aforementioned reaction is conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to 15 about 80°C, for a time period of about 30 minutes to about 6 hours. Preferably, the aforementioned reaction is conducted in the absence of any aforementioned base.

Alternatively, compounds of formulae IVm and IVn, respectively, can be prepared by reacting a compound of formula VI with a compound of formula

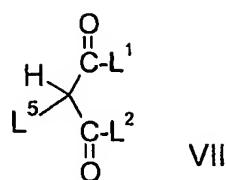


20 (i.e., a compound of formulae Vm' and Vn', respectively):



wherein L³ is preferably halo, most preferably chloro. The aforementioned reaction can be conducted optionally in the presence of a tertiary amine base in a suitable solvent. Suitable 25 bases include *N,N*-dimethylaniline or pyridine. Suitable solvents include a hydrocarbon solvent (benzene or toluene), tetrahydrofuran or methylene chloride, preferably aromatic hydrocarbon solvent, such as benzene or toluene. The aforesaid reaction can be conducted at a temperature of about -10°C to about 50°C, preferably about 0°C to about 30°C, for a time period of about 30 minutes to about 12 hours. Preferably, the aforementioned reaction is conducted in the absence of any aforementioned base.

30 A compound of formula VI can be prepared by reacting a compound of formula H₂N-A-Y-B-G with a compound of the formula VII:



wherein L^1 and L^2 are leaving groups, such as methoxy, ethoxy, or benzyloxy; preferably ethoxy; and L^5 is a leaving group, such as halo, *para*-tolylsulfonyloxy (OTs) or methylsulfonyloxy (OMs); preferably halo; most preferably chloro or bromo. The aforesaid reaction can be performed either neat or in the presence of a suitable solvent, preferably neat, in the presence of a suitable base. Suitable solvents include tetrahydrofuran or dimethylformamide. Suitable bases include a weak tertiary amine base, preferably tertiary aniline bases, most preferably N,N-dimethylaniline. Preferably, the aforementioned reaction is conducted at a temperature of about 23°C to about 100°C, preferably about 50°C to about 10 90°C, for a time period of about 30 minutes to about 24 hours.

In the aforesaid reactions, each of the compounds of formulae IVj-IVl may be isolated, but are preferably carried on to the next step without isolation. Thus, in Scheme 1, the compound of formulae IIIj-IIIl is preferably prepared in a one-pot preparation from a compound of the formula VI.

15 If the compounds of the formulae IVj-IVl are not isolated, the suitable solvent for the one-pot preparation is dimethylformamide, tetrahydrofuran, or alcohol. Preferably, the one-pot preparation is conducted in the presence of a suitable base, such as NaH, Et₃N or an alkoxide base. The aforesaid reaction can be conducted at a temperature of about 40°C to about 90°C, preferably about 60°C to about 80°C. The aforesaid reaction can be conducted for a time 20 period of about 15 minutes to about 12 hours.

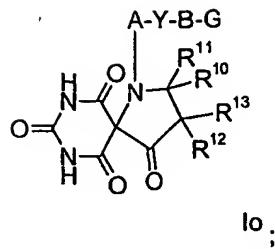
The compounds of formula H₂N-A-Y-B-G are commercially available or can be made by methods well known to those skilled in the art. Alternatively, the compounds of formula H₂N-A-Y-B-G can be prepared as described in Scheme 3.

25 A compound of the formula VII can be made by methods well known in the art such as those described in PCT Patent Publication WO 98/58925 or reviewed in The Organic Chemistry of Drug Synthesis, D. Lednicer and L. A. Mitscher, Volume 1, pages 167 to 277 and references therein. Each of the above referenced publications and applications is hereby incorporated by reference in its entirety.

30 Compounds of the formula II are commercially available or can be made by methods well known to those skilled in the art.

Scheme 2 refers to the preparation of a compound of the formula I, wherein the heterocyclic ring X has the formula o, i.e., a compound of formula I_o. Referring to Scheme 2, a compound of formula I_o:

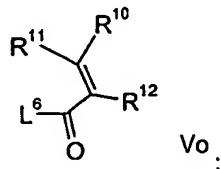
-47-



can be prepared by reacting a compound of the formula IIlo, wherein L¹ and L² are leaving groups, with a urea of formula II (i.e., H₂N-(CO)-NH₂) in the presence of a suitable base in a polar solvent. Suitable leaving groups include methoxy, ethoxy, or benzyloxy, preferably ethoxy. Suitable bases include alkoxide bases, such as sodium methoxide, sodium ethoxide and potassium *tert*-butoxide, preferably sodium ethoxide. Suitable solvents include tetrahydrofuran, dimethylformamide, or alcohols (such as ethanol), preferably tetrahydrofuran or dimethylformamide. The aforesaid reaction is conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 5 minutes to 10 about 8 hours.

A compound of formula IIlo can be prepared by reacting a compound of formula IVo, wherein L³ is a leaving group, with a suitable base in a polar solvent. Suitable leaving groups include alkoxy (such as methoxy, ethoxy, or benzyloxy) or halo; preferably methoxy or ethoxy. Suitable bases include alkoxide bases, preferably sodium methoxide or sodium ethoxide. 15 Suitable solvents include alcohols, preferably ethanol. The aforesaid reaction can be conducted at a temperature of about 0°C to about 90°C, preferably of about 60°C to about 90°C, for a period of about 1 hour to about 36 hours.

A compound of formula IVo can be prepared by reacting a compound of formula VI with the compound of formula Vo:



20 wherein L⁶ is a suitable leaving group, in a suitable solvent. Suitable L⁶ includes alkoxy or halo, such as chloro; preferably alkoxy; more preferably methoxy or ethoxy. Optionally, the aforesaid reaction may be conducted in the presence of a suitable tertiary amine base, such as triethylamine, *N,N*-dimethylaniline, or pyridine. Suitable solvents, include hydrocarbon 25 solvents (benzene or toluene), tetrahydrofuran, or methylene chloride, preferably tetrahydrofuran. Preferably, the aforementioned reaction is conducted in tetrahydrofuran or dimethylformamide, in the presence of the aforementioned suitable tertiary amine base. The aforesaid reaction may be conducted at a temperature of about 20°C to about 90°C, preferably about 50°C to about 80°C, for a time period of about 30 minutes to about 6 hours.

In the aforesaid reactions, a compound of formula IVo may be isolated, but is preferably carried on to the next step without isolation. Thus, in Scheme 1, a compound of formula IIlo is preferably prepared in a one-pot preparation from a compound of the formula VI.

5 If the compounds of the formulae IVo are not isolated, the suitable solvent for the one-pot preparation is dimethylformamide, tetrahydrofuran, or alcohols, preferably alcohol, such as ethanol. The aforesaid one pot preparation is suitably conducted at a temperature of about 0°C to about 70°C, preferably about 23°C to about 60°C, for a time period of about 30 minutes to about 24 hours.

10 A compound of formula VI can prepared by reacting a compound of formula $H_2N\text{-A-Y-B-G}$ with a compound of the formula VII as described Scheme 1.

Scheme 3 refers to the preparation of compounds of the formula $H_2N\text{-A-Y-B-G}$, which are intermediates useful in the preparation of compounds of formula I in Schemes 1 and 2. Referring to Scheme 3, compounds of formula $H_2N\text{-A-Y-B-G}$ can be prepared by reacting a 15 compound of formula VIII with a reducing agent, such as tin II chloride, in the presence of a suitable acid, such as hydrochloric acid, in a polar protic solvent. Suitable solvents include an alcoholic solvent, water, or mixtures thereof, preferably a mixture of ethanol and water. The aforesaid reaction can be conducted at a temperature of about 40°C to about 100°C for a period of about 1 to about 12 hours.

20 Alternatively, the compounds of formula $H_2N\text{-A-Y-B-G}$ can be prepared by reacting a compound of formula VIII with hydrogen gas, at a pressure between atmospheric pressure and 50 psi, in the presence of a catalyst and a polar solvent. Suitable catalysts include a palladium or platinum catalyst, preferably Adams catalyst (i.e., platinum oxide), or palladium adsorbed on charcoal. Suitable solvents include an alcoholic solvent, preferably methanol. 25 The aforesaid reaction can be conducted at a temperature of about 20°C to about 50°C, preferably about 23°C, for a period of about 30 minutes to about 6 hours.

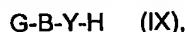
A compound of the formula VIII, wherein Y is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{O}-$, $>\text{NR}^{14}$, $-\text{CH}_2[\text{N}(\text{R}^{14})]-$ or $-\text{SO}_2[\text{N}(\text{R}^{14})]-$, can be prepared by reacting a compound of formula X, wherein the group L^7 is fluoro or chloro, with a compound of the formula:

30 G-B-Y-H (IX)

wherein Y is $-\text{O}-$, $-\text{S}-$, $-\text{CH}_2\text{S}-$, $-\text{CH}_2\text{O}-$, $>\text{NR}^{14}$, $-\text{CH}_2[\text{N}(\text{R}^{14})]-$ or $-\text{SO}_2[\text{N}(\text{R}^{14})]-$, in the presence of a base in a polar aprotic solvent. Suitable bases include an alkali metal hydride base; preferably sodium hydride. Suitable solvents include dimethylformamide, tetrahydrofuran or 1,2-dimethoxyethane; preferably dimethylformamide. The aforesaid reaction can be 35 conducted at a temperature of about 40°C to about 140°C, preferably about 80°C to about 120°C, for about 1 hour to about 24 hours.

Alternatively, the aforesaid compound of formula VIII, wherein Y is -O-, -S-, -CH₂S-, -CH₂O-, >NR¹⁴, -CH₂[N(R¹⁴)]- or -SO₂[N(R¹⁴)]-, can be prepared in presence of an alkali metal hydroxide base, preferably potassium hydroxide, optionally in the presence of a phase transfer catalyst, such as a quaternary ammonium or phosphonium salt, preferably 5 tetrabutylammonium bromide, in an aromatic hydrocarbon solvent. Preferably the solvent is benzene or toluene. The aforesaid reaction can be conducted at a temperature of about 0°C to about 120°C, preferably at about 23°C, for about 1 hour to about 12 hours.

Alternatively, the aforesaid compound of formula VIII, wherein Y is -O-, -S-, -CH₂S-, -CH₂O-, >NR¹⁴, -CH₂[N(R¹⁴)]- or -SO₂[N(R¹⁴)]-, can be prepared by reacting a compound of 10 formula X, wherein the group L⁷ is chloro or fluoro, with a compound of the formula:



wherein Y is -O-, -S-, -CH₂S-, >-SO₂[N(R¹⁴)]-, in the presence of a base under phase transfer catalysis. Suitable bases include an alkali metal hydroxide ammonium salts base, preferably potassium hydroxide. Suitable catalysts include a gesturing preferably teterbutylammonium 15 bromide. Suitable solvents include toluene or benzine. The aforesaid reaction can be conducted at a temperature of about 20 °C to about 80 °C, for about 6 hours to about 24 hours.

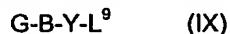
A compound of formula VIII, wherein the group Y is in an oxidized state, i.e., >SO₂, >S=O, -CH₂SO-, -CH₂SO₂-, SOCH₂- or -SO₂CH₂-, can be prepared by reacting a 20 corresponding compound of formula VIII, wherein the group Y is in a corresponding lower oxidation state, with a suitable oxidizing agent in a solvent. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is >SO₂ and >S=O is a compound of formula VIII, wherein the group Y is S. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is -CH₂SO₂- and -CH₂SO- is a 25 compound of formula VIII, wherein the group Y is -CH₂S-. The corresponding lower oxidation state for each compound of formula VIII, wherein the group Y is -SO₂CH₂- and -SOCH₂- is a compound of formula VIII, wherein the group Y is -SCH₂. Suitable oxidizing agents include a peroxy acid, preferably peracetic acid, or an organic peroxide, preferably *m*-chloroperoxybenzoic acid or *tert*-butyl hydroperoxide. Suitable solvents include methylene 30 chloride or alcohol, such as ethanol. The aforesaid reaction can be conducted at a temperature of about -10°C to about 30°C, for about 1 hour to about 8 hours.

A compound of the formula VIII, wherein Y is -OCH₂-, -SCH₂- or -[NR¹⁴](CH₂)-, respectively, can be prepared by reacting a compound of the formula X, wherein the group L⁷ is L⁸-CH₂- and wherein the group L⁸ is halo, such as chloro, bromo, iodo, mesyloxy (MsO), or 35 tosyloxy (TsO), with a compound of formula:



wherein the group M is -O-, -S-, or -NR¹⁴, respectively, in the presence of a base in a polar aprotic solvent. Suitable bases include an alkali metal carbonate base, preferably potassium carbonate or cesium carbonate. Suitable solvents include dimethylformamide or tetrahydrofuran. The aforesaid reaction can be conducted at a temperature of about 23°C to 5 about 80°C, preferably about 20°C to about 50°C, for about 1 to about 24 hours.

A compound of the formula VIII, wherein Y is >C=O, -CH=CH- or -C≡C-, can be prepared by reacting a compound of formula X, wherein the group L⁷ is dihydroxyborane; zinc halide, such as zinc chloride; or trialkyl tin, such as tributyl tin, with a compound of the formula:



10 wherein Y is >C=O, -CH=CH- or -C≡C-; and wherein the group L⁹ is halo; preferably chloro, bromo or iodo; in the presence of a catalyst in a solvent. Suitable catalysts include a palladium or nickel catalyst, preferably tetrakis triphenyl phosphine palladium (0) (Pd(PPh₃)₄). Suitable solvents include toluene, tetrahydrofuran, dimethylformamide, or dimethylsulfoxide. The aforesaid reaction can be conducted at a temperature of about 23°C to about 110°C, for a 15 period of about 1 hour to about 24 hours. Such reactions can be facilitated by the presence of a copper salt, such as cuprous iodide or cuprous bromide.

Alternatively, a compound of the formula VIII, wherein Y is -C≡C-, can be prepared by reacting a compound of formula X, wherein L⁷ is halo or triflate, preferably bromo or iodo, with a compound of the formula:



in the presence of a base, such as a trialkylamine base, preferably triethylamine and a palladium catalyst, preferably Pd(PPh₃)₄ in a solvent. Suitable solvents include tetrahydrofuran or dimethylformamide. The aforesaid reaction can be conducted at a temperature of about 23°C to about 60°C for a period of about 1 to about 24 hours.

25 Compounds of the formulae IX (i.e., compounds of the formulae G-B-Y-H, G-B-M-H, or G-B-Y-L⁹) are either commercially available or can be prepared by methods as described in Scheme 4. Referring to Scheme 4, compounds of formula G-B-Y-H can be prepared by reacting compounds of formula XI, wherein Z is a suitable protecting group such as methyl or benzyl with the appropriate protecting group removing agent, in the presence of an acidic 30 solvent, preferably a strongly acidic solvent. Suitable protecting group removing agents include sulfur-containing amino acid such as methionine, preferably dl methionine. Suitable acidic solvents include sulfonic acid solvent preferably methanesulfonic acid. The aforesaid reaction can be conducted at a temperature of about 0°C to about 100°C, preferably about 23°C to about 50°C. The aforesaid reaction can be conducted for a period of about 4 hours to 35 about 48 hours, preferably about 12 hours to about 24 hours.

In the case where the Z protecting group is benzyl, the suitable protecting group removing agents include H₂ gas (between 10 psi and 500 psi, preferably 50 psi) in the

presence of a suitable catalyst in a suitable solvent optionally in the presence of acid. Suitable catalysts include Pd/C or Pd(OH)₂ on carbon. Suitable solvents include a polar solvent, preferably methanol or ethanol. Suitable acids include acetic acid. The aforesaid reaction can be conducted at about 20°C. The aforesaid reaction can be conducted for about 1 hour to 5 about 48 hours, preferably about 6 hours.

Alternatively, compounds of formula G-B-Y-H can be prepared by reacting compounds of formula XI, wherein Z is an methyl group, with a methyl group removing agent, in the presence of a Lewis acid and a polar aprotic solvent. Suitable methyl protecting group removing agents include a quaternary ammonium halide salts, such as a quaternary 10 ammonium iodide salt, preferably tetrabutylammonium iodide. Suitable Lewis acids include boron halide Lewis acid, preferably boron trichloride. Suitable polar aprotic solvents include chlorinated hydrocarbon solvent, preferably methylene chloride. The aforesaid reaction can be conducted at a temperature of about -78 °C to about 50°C, preferably about -78 °C to about 15 23°C. The aforesaid reaction can be conducted for a period of about 1 hours to about 24 hours, preferably about 1 hours to about 6 hours.

In the case where the Z protecting group is methyl, the suitable protecting group removing agents include a fluoride containing agent in a polar aprotic solvent. Suitable fluoride containing agents include tetrabutyl ammonium fluoride. Suitable polar aprotic solvents include tetrahydrofuran. The aforesaid reaction can be conducted at about 0°C to about 50°C, 20 preferably at about 20°C. The aforesaid reaction can be conducted for a period of about 1 hour to about 24 hours, preferably about 4 hours.

Compounds of the formulae XI, wherein G is alkyl, can be prepared by reacting a compound of formula XII, wherein Z is a benzyl or methyl group, with an alkylating agent, in the presence of a base and a polar aprotic solvent. Suitable alkylating agents include alkyl 25 halide or alkyl sulfonate ester, preferably an alkyl iodide. Suitable bases include an alkali metal hydride, preferably sodium hydride, or an alkali metal carbonate, preferably potassium carbonate. Suitable polar aprotic solvents include DMF, *N,N*-dimethyl acetamide or NMP, preferably DMF. The aforesaid reaction can be conducted at a temperature of about 0°C to about 100°C, preferably about 0°C to about 50°C. The aforesaid reaction can be conducted 30 for a period of about 1 hour to about 24 hours, preferably about 1 hours to about 6 hours.

Compounds of the formulae XI, wherein G is aryl, can be prepared by reacting a compound of formula XII, wherein Z is a benzyl or methyl group, with an arylating agent, in the presence of a base and a polar aprotic solvent, optionally in the presence of a catalyst. Suitable arylating agents include aryl halide, aryl tosylate; preferably aryl fluoride, aryl bromide 35 or aryl iodide. Suitable bases include an alkali metal hydride, preferably sodium hydride, or an alkali metal carbonate, preferably potassium carbonate. Suitable polar aprotic solvents include DMF, *N,N*-dimethyl acetamide or NMP, preferably DMF. Suitable catalysts include copper

catalysts such as copper (I) or copper (0) catalyst, preferably Cu_2O or copper bronze. The aforesaid reaction can be conducted at a temperature of about 0°C to about 180°C, preferably about 160°C. The aforesaid reaction can be conducted for a period of about 1 hour to about 24 hours, preferably about 6 hours to about 24 hours.

5 Other suitable arylating agents include aryl boronic acid. Such arylating agents are used in the preparation of compounds of the formula XI, wherein G is aryl, in the presence of copper (II) catalyst, a base, and a water scavengers, in polar aprotic solvent. Suitable catalysts include $\text{Cu}(\text{OAc})_2$. Suitable bases include amines, such as tertiary amines or aromatic amines, preferably triethylamine or pyridine. Suitable water scavenger include 4A
10 molecular sieves. Suitable polar aprotic solvents include methylene chloride or DMSO. The aforesaid reaction can be conducted under an atmosphere of air or dry oxygen at a temperature of about 0°C to about 50°C, preferably about 23°C. The aforesaid reaction can be conducted for a period of about 1 hour to about 21 days, preferably about 12 hours to about 2 days.

15 Compounds of the formulae XI, wherein G is heteroaryl, can be prepared by reacting compounds of formula XII, wherein Z is a benzyl or methyl group, with a heteroarylation agent, in the presence of a base and a polar aprotic solvent, optionally in the presence of a catalyst. Suitable heteroarylation agents include heteroaryl halide, heteroaryl tosylate; preferably heteroaryl fluoride, heteroaryl chloride, or heteroaryl bromide. Suitable bases include an alkali metal hydride, preferably sodium hydride, or an alkali metal carbonate, preferably potassium carbonate. Suitable polar aprotic solvents include DMF, *N,N*-dimethyl acetamide or NMP, preferably DMF. Suitable catalysts include copper catalysts such as copper (I) or copper (0) catalyst, preferably Cu_2O or copper bronze. The aforesaid reaction can be conducted at a temperature of about 0°C to about 180°C, preferably about 80-160°C. The aforesaid reaction
20 can be conducted for a period of about 1 hour to about 24 hours, preferably about 1 hours to about 8 hours.

25 Other suitable heteroarylation agents include heteroaryl boronic acid. Such heteroarylation agent is used in the preparation of compounds of the formula XI, wherein G is heteroaryl, in the presence of copper (II) catalyst, a base, and a water scavengers, in polar aprotic solvent. Suitable catalysts include $\text{Cu}(\text{OAc})_2$. Suitable bases include amines, such as tertiary amines or aromatic amines, preferably triethylamine or pyridine. Suitable water scavenger include 4A molecular sieves. Suitable polar aprotic solvents include methylene chloride or DMSO. The aforesaid reaction can be conducted under an atmosphere of air or dry oxygen at a temperature of about 0°C to about 50°C, preferably about 23°C. The aforesaid reaction
30 can be conducted for a period of about 1 hour to about 21 days, preferably about 12 hours to about 2 days.

Compounds of the formulae X, IX, and XII are either commercially available or are well known and can be prepared by methods known to those skilled in the art.

The compounds of the formula I, which are basic in nature, are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts 5 must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base 10 compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition 15 salts of the base compounds of this invention are those which form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3- 20 naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical 25 bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an 30 aqueous solution containing the desired pharmacologically acceptable cations and then evaporating the resulting solution to dryness, preferably under reduced pressure.

Alternatively, these salts may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together and then evaporating the 35 resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

BIOLOGICAL ASSAYS

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit metalloproteinases or mammalian reproxins and, consequently, demonstrate their 5 effectiveness for treating diseases characterized by metalloproteinase activity is shown by the following *in vitro* and *in vivo* assay tests.

MMP Assays

MMP-13 selective inhibitors can be identified by screening the inhibitors of the present invention through the MMP fluorescence assays described below and selecting those agents 10 with MMP-13/MMP-X inhibition IC₅₀ ratios of 100 or greater and potency of less than 100 nM, where MMP-X refers to one or more other MMPs.

Non-selective collagenase inhibitors as used herein, unless otherwise mentioned, refer to agents which exhibit less than a 100 fold selectivity for the inhibition of MMP-13 enzyme 15 activity over MMP-X enzyme activity or a potency of more than 100nM as defined by the IC₅₀ results from the MMP-13/MMP-X fluorescence assays described below.

The ability of collagenase inhibitors to inhibit collagenase activity is well known in the art. The degree of inhibition of a particular MMP for several compounds has been well documented in the art and those skilled in the art will know how to normalize different assay results to those 20 assays reported herein. The following assays may be used to identify matrix metalloproteinase inhibitors.

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin. The amount of trypsin is optimized for each lot of collagenase-1 but a typical reaction uses the following ratio: 5 µg trypsin 25 per 100 µg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 mg/10 mg trypsin) of soybean trypsin inhibitor is added.

Stock solutions (10 mM) of inhibitors are made up in dimethylsulfoxide and then diluted using the following scheme:

10 mM -----> 120 µM -----> 12 µM -----> 1.2 µM -----> 0.12 µM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of 30 a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D7-D12 and negative controls (no enzyme, no inhibitors) are set in wells D1-D6.

Collagenase-1 is diluted to 240 ng/ml and 25 µl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 60 ng/ml.

35 Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is made as a 5 mM stock in dimethylsulfoxide and then diluted to 20 µM in assay buffer. The assay is initiated by the addition of 50 µl substrate per well of the microfluor plate to give a final concentration of 10 µM.

Fluorescence readings (360 nm excitation, 460 nm emission) are taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence versus time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (at least five fold over the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC₅₀ values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120-minute data. Data is plotted as inhibitor concentration versus % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC₅₀'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC₅₀'s are reported to be less than 0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

15 Human recombinant 72 kD gelatinase (MMP-2, gelatinase A) is activated for 16-18 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 4°C, rocking gently.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μM ZnCl₂ and 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

$$10 \text{ mM} \rightarrow 120 \text{ μM} \rightarrow 12 \text{ μM} \rightarrow 1.2 \text{ μM} \rightarrow 0.12 \text{ μM}$$

Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. 25 As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μM → 3 μM → 0.3 μM → 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

30 Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.34 nM).

A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μM. The assay is initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 10 μM substrate. At time zero, 35 fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by 5 fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC_{50} 's are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Stromelysin Activity (MMP-3)

Human recombinant stromelysin (MMP-3, stromelysin-1) is activated for 20-22 hours 10 with 2 mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37°C.

10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 150 mM NaCl, 10 mM CaCl₂ and 0.05% BRIJ-35 (vol./vol.)) using the following scheme:

15 10 mM → 120 μM → 12 μM → 1.2 μM → 0.12 μM

Further dilutions are made as necessary following this same scheme. A minimum of four 20 inhibitor concentrations for each compound are performed in each assay. 25 μL of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μL, final concentrations of inhibitor are the result of a further 25 1:4 dilution (i.e. 30 μM → 3 μM → 0.3 μM → 0.03 μM, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

Activated enzyme is diluted to 200 ng/mL in assay buffer, 25 μL per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 50 ng/mL (0.875 nM).

30 A ten mM dimethylsulfoxide stock solution of substrate (Mca-Arg-Pro-Lys-Pro-Val-Glu-Nva-Trp-Arg-Lys(Dnp)-NH₂) is diluted in assay buffer to 6 μM. The assay is initiated by addition of 50 μL of diluted substrate yielding a final assay concentration of 3 μM substrate. At time zero, fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive 35 Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC_{50} determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the 35 data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration

versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of Human 92 kD Gelatinase (MMP-9)

Inhibition of 92 kD gelatinase (MMP-9) activity is assayed using the Mca-Pro-Leu-Gly-
5 Leu-Dpa-Ala-Arg-NH₂ substrate (10 μ M) under similar conditions as described above for the inhibition of human collagenase (MMP-1).

Human recombinant 92 kD gelatinase (MMP-9, gelatinase B) is activated for 2 hours with 1mM p-aminophenyl-mercuric acetate (from a freshly prepared 100 mM stock in 0.2 N NaOH) at 37 C.

10 10 mM dimethylsulfoxide stock solutions of inhibitors are diluted serially in assay buffer (50 mM TRIS, pH 7.5, 200 mM NaCl, 5 mM CaCl₂, 20 μ M ZnCl₂, 0.02% BRIJ-35 (vol./vol.)) using the following scheme:

10 mM \longrightarrow 120 μ M \longrightarrow 12 μ M \longrightarrow 1.2 μ M \longrightarrow 0.12 μ M

15 Further dilutions are made as necessary following this same scheme. A minimum of four inhibitor concentrations for each compound are performed in each assay. 25 μ L of each concentration is then added to triplicate wells of a black 96 well U-bottomed microfluor plate. As the final assay volume is 100 μ L, final concentrations of inhibitor are the result of a further 1:4 dilution (i.e. 30 μ M \longrightarrow 3 μ M \longrightarrow 0.3 μ M \longrightarrow 0.03 μ M, etc.). A blank (no enzyme, no inhibitor) and a positive enzyme control (with enzyme, no inhibitor) are also prepared in triplicate.

20 Activated enzyme is diluted to 100 ng/mL in assay buffer, 25 μ L per well is added to appropriate wells of the microplate. Final enzyme concentration in the assay is 25 ng/mL (0.27 nM).

25 A five mM dimethylsulfoxide stock solution of substrate (Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH₂) is diluted in assay buffer to 20 μ M. The assay is initiated by addition of 50 μ L of diluted substrate yielding a final assay concentration of 10 μ M substrate. A zero time fluorescence reading (320 excitation; 390 emission) is immediately taken and subsequent readings are taken every fifteen minutes at room temperature with a PerSeptive Biosystems CytoFluor Multi-Well Plate Reader with the gain at 90 units.

30 The average value of fluorescence of the enzyme and blank are plotted versus time. An early time point on the linear part of this curve is chosen for IC₅₀ determinations. The zero time point for each compound at each dilution is subtracted from the latter time point and the data then expressed as percent of enzyme control (inhibitor fluorescence divided by fluorescence of positive enzyme control x 100). Data is plotted as inhibitor concentration versus percent of enzyme control. IC₅₀'s are defined as the concentration of inhibitor that gives a signal that is 50% of the positive enzyme control.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2 mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5 mM calcium chloride, 20 μ M zinc chloride, 0.02% brij). Twenty-five 5 microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1):
10 Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μ M, 3 μ M, 0.3 μ M and 0.03 μ M.

15 Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH₂) is prepared as for inhibition of human collagenase (MMP-1) and 50 μ l is added to each well to give a final assay concentration of 10 μ M. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC₅₀'s are determined as per inhibition of human collagenase (MMP-1). If IC₅₀'s are reported to be less than 0.03 μ M, inhibitors are then assayed at final concentrations of 0.3 μ M, 20 0.03 μ M, 0.003 μ M and 0.0003 μ M.

Collagen film MMP-13 Assay

Rat type I collagen is radiolabeled with ¹⁴C acetic anhydride (T.E. Cawston and A.J. Barrett, Anal. Biochem., 99, 340-345 (1979)) and used to prepare 96 well plates containing radiolabeled collagen films (Barbara Johnson-Wint, Anal. Biochem., 104, 175-181 (1980)).
25 When a solution containing collagenase is added to the well, the enzyme cleaves the insoluble collagen which unwinds and is thus solubilized. Collagenase activity is directly proportional to the amount of collagen solubilized, determined by the proportion of radioactivity released into the supernatant as measured in a standard scintillation counter. Collagenase inhibitors are, therefore, compounds which reduce the radioactive counts released with respect to the 30 controls with no inhibitor present. One specific embodiment of this assay is described in detail below.

For determining the selectivity of compounds for MMP-13 versus MMP-1 using collagen as a substrate, the following procedure is used. Recombinant human proMMP-13 or proMMP-1 is activated according to the procedures outlined above. The activated MMP-13 or 35 MMP-1 is diluted to 0.6 ug/ml with buffer (50 mM Tris pH 7.5, 150 mM NaCl, 10 mM CaCl₂, 1 μ M ZnCl₂, 0.05% Brij-35, 0.02% sodium azide).

Stock solutions of test compound (10mM) in dimethylsulfoxide are prepared. Dilutions of the test compounds in the Tris buffer, above, are made to 0.2, 2.0, 20, 200, 2000 and 20000 nM.

100 μ l of appropriate drug dilution and 100 μ l of diluted enzyme are pipetted into wells 5 of a 96 well plate containing collagen films labeled with 14 C-collagen. The final enzyme concentration is 0.3 μ g/ml while the final drug concentration is 0.1, 1.0, 10, 100, 1000 nM. Each drug concentration and control is analyzed in triplicate. Triplicate controls are also run for the conditions in which no enzyme is present and for enzyme in the absence of any compound.

10 The plates are incubated at 37°C for a time period such that around 30 - 50% of the available collagen is solubilized - determined by counting additional control wells at various time points. In most cases around 9 hours of incubation are required. When the assay has progressed sufficiently, the supernatant from each well is removed and counted in a scintillation counter. The background counts (determined by the counts in the wells with no 15 enzyme) are subtracted from each sample and the % release calculated in relation to the wells with enzyme only and no inhibitor. The triplicate values for each point are averaged and the data graphed as percent release versus drug concentration. IC₅₀'s are determined from the point at which 50% inhibition of release of radiolabeled collagen is obtained.

20 To determine the identity of the active collagenases in cartilage conditioned medium, assays were conducted using collagen as a substrate, cartilage conditioned medium containing collagenase activity and inhibitors of varying selectivity. The cartilage conditioned medium was collected during the time at which collagen degradation was occurring and thus is representative of the collagenases responsible for the collagen breakdown. Assays were conducted as outlined above except that instead of using recombinant MMP-13 or 25 recombinant MMP-1, cartilage conditioned medium was the enzyme source.

IL-1 Induced Cartilage Collagen Degradation From Bovine Nasal Cartilage

30 This assay uses bovine nasal cartilage explants which are commonly used to test the efficacy of various compounds to inhibit either IL-1 induced proteoglycan degradation or IL-1 induced collagen degradation. Bovine nasal cartilage is a tissue that is very similar to articular cartilage, i.e. chondrocytes surrounded by a matrix that is primarily type II collagen and aggrecan. The tissue is used because it: (1) is very similar to articular cartilage, (2) is readily available, (3) is relatively homogeneous and (4) degrades with predictable kinetics after IL-1 stimulation.

35 Two variations of this assay have been used to assay compounds. Both variations give similar data. The two variations are described below:

Variation 1

Three plugs of bovine nasal cartilage (approximately 2 mm diameter x 1.5 mm long) are placed into each well of a 24 well tissue culture plate. One ml of serumless medium is then added to each well. Compounds are prepared as 10 mM stock solutions in DMSO and 5 then diluted appropriately in serumless medium to final concentrations, e.g., 50, 500 and 5000 nM. Each concentration is assayed in triplicate.

Human recombinant IL-1 α (5ng/mL) (IL-1) is added to triplicate control wells and to each well containing drug. Triplicate control wells are also set up in which neither drug nor IL-1 are added. The medium is removed and fresh medium containing IL-1 and the appropriate 10 drug concentrations is added on days 6, 12, 18 and 24 or every 3 - 4 days if necessary. The media removed at each time point is stored at -20°C for later analysis. When the cartilage in the IL-1 alone wells has almost completely resorbed (about day 21), the experiment is terminated. The medium, is removed and stored. Aliquots (100 μ l) from each well at each 15 time point are pooled, digested with papain and then analyzed for hydroxyproline content. Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot.

Variation 2

The experimental set-up is the same as outlined above in Variation 1, until day 12. 20 On day 12, the conditioned medium from each well is removed and frozen. Then one ml of phosphate buffered saline (PBS) containing 0.5 μ g/ml trypsin is added to each well and incubation continued for a further 48 hours at 37°C. After 48 hours incubation in trypsin, the PBS solution is removed. Aliquots (50 μ l) of the PBS/trypsin solution and the previous two time points (days 6 and 12) are pooled, hydrolyzed and hydroxyproline content determined. 25 Background hydroxyproline (average of wells with no IL-1 and no drug) is subtracted from each data point and the average calculated for each triplicate. The data is then expressed as a percent of the IL-1 alone average value and plotted. The IC₅₀ is determined from this plot. In this variation, the time course of the experiment is shortened considerably. The addition of trypsin for 48 hours after 12 days of IL-1 stimulation likely releases any type II collagen that 30 has been damaged by collagenase activity but not yet released from the cartilage matrix. In the absence of IL-1 stimulation, trypsin treatment produces only low background levels of collagen degradation in the cartilage explants.

Inhibition of TNF Production

The ability or inability of the compounds or the pharmaceutically acceptable salts thereof 35 to inhibit the production of TNF is shown by the following in vitro assay:

Human Monocyte Assay

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 5 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180 μ l of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100 ng/ml final concentration) gave a final volume of 200 μ l. 10 All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO₂ incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF α using the R&D ELISA Kit.

Aggrecanase Assay

Primary porcine chondrocytes from articular joint cartilage are isolated by sequential 15 trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at 2 X 10^5 cells per well into 48 well plates with 5 μ Ci / ml ³⁵S (1000 Ci/mmol) sulphur in type I collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C, under an atmosphere of 5% CO₂.

20 The night before initiating the assay, chondrocyte monolayers are washed two times in DMEM/ 1% PSF/G and then allowed to incubate in fresh DMEM /1% FBS overnight.

The following morning chondrocytes are washed once in DMEM/1%PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions.

Media and dilutions can be made as described in the Table below.

Control Media	DMEM alone (control media)
IL-1 Media	DMEM + IL-1 (5 ng/ml)
Drug Dilutions	<p>Make all compounds stocks at 10 mM in DMSO.</p> <p>Make a 100 μM stock of each compound in DMEM in 96 well plate. Store in freezer overnight.</p> <p>The next day perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM and 50 nM.</p> <p>Aspirate final wash from wells and add 50 μl of compound from above dilutions to 450 μl of IL-1 media in appropriate wells of the 48 well plates.</p> <p>Final compound concentrations equal 500 nM, 50 nM and 5 nM.</p> <p>All samples completed in triplicate with Control and IL-1 alone samples on each plate.</p>

Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and Control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 μ l) followed by compound (50 μ l) so as to initiate the 5 assay. Plates are incubated at 37°C, with a 5% CO₂ atmosphere.

At 40-50 % release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (9-12 hours). Media is removed from all wells and placed in scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μ l of papain 10 digestion buffer (0.2 M Tris, pH 7.0, 5 mM EDTA, 5 mM DTT and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added and samples counted (LSC).

The percent of released counts from the total present in each well is determined. 15 Averages of the triplicates are made with control background subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

The compounds of the present invention that were tested all have IC₅₀'s in at least one of the above assays of less than 100 μ M preferably less than 100nM. Certain preferred 20 groups of compounds possess differential selectivity toward the various MMPs or ADAMs. One group of preferred compounds possesses selective activity towards MMP-13 over MMP-1. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-3 and MMP-7. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-3, MMP-7 and MMP-17. Another preferred group 25 of compounds possesses selective activity towards MMP-13 over MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-14. Another preferred group of compounds possesses selective activity towards MMP-13 over MMP-12 and MMP-14.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases, a variety of conventional routes may be used including oral, parenteral (e.g., 30 intravenous, intramuscular or subcutaneous), buccal, anal and topical. In general, the compounds of the invention (hereinafter also known as the active compounds) will be administered at dosages of about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. Preferably the active compound will be administered orally or parenterally. However, some variation in dosage will necessarily occur depending on the 35 condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

5 For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as
10 magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring
15 agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and
20 intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The
25 oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3
30 divided doses.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of
35 the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or

other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a 5 powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

For topical ocular administration, direct application to the affected eye may be employed in the form of a formulation as eyedrops, aerosol, gels or ointments, or can be incorporated into collagen (such as poly-2-hydroxyethylmethacrylate and co-polymers thereof), or a hydrophilic 10 polymer shield. The materials can also be applied as a contact lens or via a local reservoir or as a subconjunctival formulation.

For intraorbital administration a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in an aqueous solution or suspension (particle size less than 10 micron) may be employed. The aqueous 15 solutions should be suitably adjusted and buffered, preferably at a pH between 5 and 8, if necessary and the liquid diluent first rendered isotonic. Small amounts of polymers can be added to increase viscosity or for sustained release (such as cellulosic polymers, Dextran, polyethylene glycol, or alginic acid). These solutions are suitable for intraorbital injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished 20 by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intraorbitally at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

As with the other routes of administration and corresponding dosage forms described herein, dosage forms intended for oral administration are also suitably formulated to provide 25 controlled-, sustained- and/or delayed release of the active ingredient. Typically, these would include delayed-release oral tablets, capsules and multiparticulates, as well as enteric-coated tablets and capsules which prevent release and adsorption of the active ingredient in the stomach of the patient and facilitate enteric delivery distal to the stomach, *i.e.*, in the intestine. Other typical oral dosage forms would include sustained-release oral tablets, capsules and 30 multiparticulates which provide systemic delivery of the active ingredient in a controlled manner over a prolonged period of time, *e.g.*, a 24-hour period. Where rapid delivery of the active ingredient is required or desirable, a controlled-release oral dosage form may be prepared in the form of a fast-dissolving tablet, which would also preferably include highly soluble salt forms of the active ingredient.

35 The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform

unless otherwise specified). Commercial reagents were utilized without further purification. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen 5 atmosphere for convenience and to maximize yields. Concentration at reduced pressure or *in vacuo* means that a rotary evaporator was used.

EXAMPLE 1

**1-[6-[1-(4-FLUORO-PHENYL)-1H-INDAZOL-5-YLOXY]-PYRIDIN-3-YL]-1,7,9-TRIAZA-
SPIRO[4.5]DECANE-6,8,10-TRIONE**

10 To a flame dried flask is added ethanol (6 mL) and freshly cut sodium metal (62.4 mg, 2.71 mmol). The solution is stirred until homogenous. Recrystallized urea (98 mg, 1.63 mmol) is added and the solution is stirred at room temperature for 5 minutes. 1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.54 mmol) is added, and the solution is heated to 80 °C for 30 minutes, then cooled to 50 °C and 15 stirred for 16 hours. The reaction is then quenched by the addition of 10 mL water, and 1N hydrochloric acid is added to adjust the pH to 5. The aqueous layer is extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers are washed with saturated sodium chloride, dried with magnesium sulfate, filtered, and concentrated under vacuum to produce crude product. This material is chromatographed on silica gel (ISCO MPLC purification, 30 minutes, 50-100% ethyl acetate gradient, Biotage flash 40s column) to provide 1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-traza-spiro[4.5]decane-6,8,10-trione.

20

**Preparation 1: 1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-
2,2-dicarboxylic acid diethyl ester**

25 1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester is prepared by dissolving 2-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-malonic acid diethyl ester (9.25 mmol) in dimethylformamide (90 mL), followed by addition of 1,3 dibromopropane (938 µL, 9.25 mmol) and cesium carbonate (6 grams, 18.5 mmol). The reaction mixture is stirred for approximately 24 hours to 48 hours. The mixture is filtered 30 through celite, and then concentrated under vacuum while heating to 55 °C to remove the dimethylformamide (azeotroping with toluene). The crude product obtained is chromatographed on silica gel (ISCO MPLC purification, 40 minutes, 0-50% ethyl acetate gradient, Biotage flash 40m column) to provide the title compound.

**Preparation 2: 2-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-
malonic acid diethyl ester**

35 2-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-malonic acid diethyl ester is prepared by combining 6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamine

(11.4 mmol), bromodiethylmalonate (11.4 mmol), and N,N-dimethylaniline (11.4 mmol) in a flame dried flask and heated to 70 °C for 3.5 hours. The mixture is cooled to room temperature, adsorbed to silica gel and chromatographed (gradient elution, ethyl acetate-hexanes) to afford the title compound.

5 Preparation 3: 6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamine

To a solution of 1-(4-Fluoro-phenyl)-5-(5-nitro-pyridin-2-yloxy)-1H-indazole (0.28 g, 0.79 mmol) in 10 mL of methanol was added 10 mL of ethyl acetate and 30 mg of platinum (IV) oxide. After shaking under 50 psi of H₂ for 3 h, the mixture was filtered through a pad of Celite and concentrated *in vacuo*, affording 0.25 g of 6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamine as a colorless solid. ¹H NMR (CD₃OD, 400 MHz): δ 8.96 (d, 1H, J = 2.8 Hz), 8.58 (dd, 1H, J = 2.8, 9.2 Hz), 8.25 (s, 1H), 7.6-7.8 (m, 3H), 7.66 (1H, d, 2.4 Hz), 7.3-7.2 (m, 3H), 7.19 (d, 1H, J = 9.2 Hz) ppm.

10 Preparation 4: 1-(4-Fluoro-phenyl)-5-(5-nitro-pyridin-2-yloxy)-1H-indazole

15 To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole (1.0 g, 3.9 mmol) in 15 mL of DMSO was added copper (II) acetate (0.71 g, 3.9 mmol), powdered 4A molecular sieves (0.2 g), 4-fluorophenylboronic acid (0.60 g, 4.3 mmol) and triethylamine (2.7 mL, 20 mmol). The resulting mixture was stirred under an oxygen atmosphere for 3 days. After filtering through a plug of Celite and silica gel, the mixture was concentrated *in vacuo*, adsorbed to silica gel, and purified by column chromatography eluting with 0-20% ethyl acetate-hexanes, affording 0.28 g of 1-(4-Fluoro-phenyl)-5-(5-nitro-pyridin-2-yloxy)-1H-indazole as a colorless syrup. ¹H NMR (CD₃OD, 400 MHz): δ 8.17 (s, 1H), 7.7-7.8 (m, 3H), 7.61 (d, 1H, J = 2.8 Hz), 7.39 (d, 1H, J = 2.0 Hz), 7.30 (m, 2H), 7.22 (m, 2H), 6.77 (1H, d, J = 8.8 Hz) ppm.

20 Preparation 5: 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole

25 To a mixture of 2-methyl-4-(5-nitro-pyridin-2-yloxy)-phenylamine (10 g, 41 mmol), potassium acetate (17 g, 160 mmol), acetic anhydride (17 g, 160 mmol) and toluene (140 mL) at 80 °C was added isoamyl nitrite (9.6 g, 82 mmol) dropwise via an addition funnel. After stirring for 24 h at 80 °C, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was treated with methanol (120 mL) containing 12 mL of concentrated ammonium hydroxide. After refluxing for 2 h, the mixture was cooled to room temperature and was concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with ethyl acetate-hexane to afford 2.2 g of 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole as an orange solid. ¹H NMR (CD₃OD, 400 MHz): δ 8.96 (d, 1H, J = 2.4 Hz), 8.56 (dd, 1H, J = 2.8, 9.2 Hz), 8.05 (s, 1H), 7.60 (1H, d, 8.8 Hz), 7.56 (m, 1H), 7.21 (dd, 1H, J = 2.0, 8.8 Hz), 7.13 (d, 1H, 9.2 Hz) ppm.

30 Preparation 6: 2-Methyl-4-(5-nitro-pyridin-2-yloxy)-phenylamine

35 To a mixture of *m*-cresol (25.8 g, 0.21 mol), 2-chloro-5-nitropyridine (30 g, 0.18 mol) and ethanol (600 mL) was added potassium hydroxide (12 g, 0.21 mol). The resulting mixture

was stirred for 12 h at reflux. After removing the ethanol *in vacuo*, the mixture was triturated with 0.1 M aqueous NaOH, filtered, and the solids were washed with 0.1 M NaOH and water, affording 43 g of 2-methyl-4-(5-nitro-pyridin-2-yloxy)-phenylamine. ¹H NMR (CDCl₃, 400 MHz): δ 9.05 (d, 1H, J = 3.2 Hz), 8.47 (dd, 1H, J = 2.8, 9.2 Hz), 6.97 (d, 1H, J = 9.2 Hz), 6.8-6.9 (m, 5 3H), 2.26 (s, 3H) ppm.

EXAMPLE 2

4-[5-[5-(6,8,10-TRIOXO-1,7,9-TRIAZA-SPIRO[4.5]DEC-1-YL)-PYRIDIN-2-YLOXY]-INDAZOL-1-YL]-BENZONITRILE

To a flame dried flask is added ethanol (6 mL) and freshly cut sodium metal (62.4 mg, 10 2.71 mmol). The solution is stirred until homogenous. Recrystallized urea (98 mg, 1.63 mmol) is added and the solution is stirred at room temperature for 5 minutes. 1-[6-[1-(4-Cyano-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.54 mmol) is added, and the solution is heated to 80 °C for 30 minutes, then cooled to 50 °C and stirred for 16 hours. The reaction is then quenched by the addition of 10 mL water, and 1N 15 hydrochloric acid is added to adjust the pH to 5. The aqueous layer is extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers are washed with saturated sodium chloride, dried with magnesium sulfate, filtered, and concentrated under vacuum to produce crude product. This material is chromatographed on silica gel (ISCO MPLC purification, 30 minutes, 50-100% ethyl acetate gradient, Biotage flash 40s column) to provide 1-[6-[1-(4-20 Cyano-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione.

Preparation 1: 1-[6-[1-(4-Cyano-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester

1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester is prepared by dissolving 2-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-malonic acid diethyl ester (9.25 mmol) in dimethylformamide (90 mL), 25 followed by addition of 1,3 dibromopropane (938 μL, 9.25 mmol) and cesium carbonate (6 grams, 18.5 mmol). The reaction mixture is stirred for approximately 24 hours to 48 hours. The mixture is filtered through celite, and then concentrated under vacuum while heating to 55 °C to remove the dimethylformamide (azeotroping with toluene). The crude product obtained 30 is chromatographed on silica gel (ISCO MPLC purification, 40 minutes, 0-50% ethyl acetate gradient, Biotage flash 40m column) to provide the title compound.

Preparation 2: 2-[6-[1-(4-Cyano-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-malonic acid diethyl ester

2-[6-[1-(4-Cyano-phenyl)-1H-indazol-5-yloxy]-pyridin-3-ylamino]-malonic acid diethyl ester can 35 be prepared by combining 4-[5-(5-Amino-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile (11.4 mmol), bromodiethylmalonate (11.4 mmol), and N,N-dimethylaniline (11.4 mmol) in a flame dried flask and heated to 70 °C for 3.5 hours. The mixture is cooled to room temperature,

adsorbed to silica gel and chromatographed (gradient elution, ethyl acetate-hexanes) to afford the title compound.

Preparation 3: 4-[5-(5-Amino-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile

5 To a solution of 4-[5-(5-Nitro-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile (0.79 mmol) in 10 mL of methanol was added 10 mL of ethyl acetate and 30 mg of platinum (IV) oxide. After shaking under 50 psi of H₂ for 3 h, the mixture was filtered through a pad of Celite and concentrated *in vacuo*, affording 0.25 g of 4-[5-(5-Amino-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile.

Preparation 4: 4-[5-(5-Nitro-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile

10 To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole (1.0 g, 3.9 mmol) in 15 mL of DMSO is added copper (II) acetate (0.71 g, 3.9 mmol), powdered 4A molecular sieves (0.2 g), 4-cyanophenylboronic acid (4.3 mmol) and triethylamine (2.7 mL, 20 mmol). The resulting mixture is stirred under an oxygen atmosphere for 3 days. After filtering through a plug of Celite and silica gel, the mixture is concentrated *in vacuo*, adsorbed to silica gel, and purified 15 by column chromatography eluting with 0-20% ethyl acetate-hexanes, affording 4-[5-(5-Nitro-pyridin-2-yloxy)-indazol-1-yl]-benzonitrile.

EXAMPLE 3

1-[6-(1-PYRIDIN-3-YL-1H-INDAZOL-5-YLOXY)-PYRIDIN-3-YL]-1,7,9-

TRIAZA-SPIRO[4.5]DECANE-6,8,10-TRIONE

20 To a flame dried flask is added ethanol (6 mL) and freshly cut sodium metal (62.4 mg, 2.71 mmol). The solution is stirred until homogenous. Recrystallized urea (98 mg, 1.63 mmol) is added and the solution is stirred at room temperature for 5 minutes. 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.54 mmol) is added, and the solution is heated to 80 °C for 30 minutes, then cooled to 50 °C and stirred for 25 16 hours. The reaction is then quenched by the addition of 10 mL water, and 1N hydrochloric acid is added to adjust the pH to 5. The aqueous layer is extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers are washed with saturated sodium chloride, dried with magnesium sulfate, filtered, and concentrated under vacuum to produce crude product. This material is chromatographed on silica gel (ISCO MPLC purification, 30 minutes, 50-100% 30 ethyl acetate gradient, Biotage flash 40s column) to provide 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione.

Preparation 1: 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester

35 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester can be prepared by dissolving 2-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester (9.25 mmol) in dimethylformamide (90 mL), followed by addition of 1,3 dibromopropane (938 µL, 9.25 mmol) and cesium carbonate (6 grams, 18.5

mmol). The reaction mixture is stirred for approximately 24 hours to 48 hours. The mixture is filtered through celite, and then concentrated under vacuum while heating to 55 °C to remove the dimethylformamide (azeotroping with toluene). The crude product obtained is chromatographed on silica gel (ISCO MPLC purification, 40 minutes, 0-50% ethyl acetate gradient, Biotage flash 40m column) to provide the title compound.

Preparation 2: 2-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester

2-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester can be prepared by combining 5-(5-Amino-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole (11.4 mmol), bromodiethylmalonate (11.4 mmol), and N,N-dimethylaniline (11.4 mmol) in a flame dried flask and heated to 70 °C for 3.5 hours. The mixture is cooled to room temperature, adsorbed to silica gel and chromatographed (gradient elution, ethyl acetate-hexanes) to afford the title compound.

Preparation 3: 5-(5-Amino-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole

To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole (0.79 mmol) in 10 mL of methanol was added 10 mL of ethyl acetate and 30 mg of platinum (IV) oxide. After shaking under 50 psi of H₂ for 3 h, the mixture was filtered through a pad of Celite and concentrated *in vacuo*, affording 0.25 g of 5-(5-Amino-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole.

Preparation 4: 5-(5-Nitro-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole

To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole (1.0 g, 3.9 mmol) in 15 mL of DMSO is added copper (II) acetate (0.71 g, 3.9 mmol), powdered 4A molecular sieves (0.2 g), 3-pyridylboronic acid (4.3 mmol) and triethylamine (2.7 mL, 20 mmol). The resulting mixture is stirred under an oxygen atmosphere for 3 days. After filtering through a plug of Celite and silica gel, the mixture is concentrated *in vacuo*, adsorbed to silica gel, and purified by column chromatography eluting with 0-20% ethyl acetate-hexanes, affording 5-(5-Nitro-pyridin-2-yloxy)-1-pyridin-3-yl-1H-indazole.

EXAMPLE 4

1-[6-(1-METHYL-1H-INDAZOL-5-YLOXY)-PYRIDIN-3-YL]-1,7,9-

30 TRIAZA-SPIRO[4.5]DECANE-6,8,10-TRIONE

To a flame dried flask is added ethanol (6 mL) and freshly cut sodium metal (62.4 mg, 2.71 mmol). The solution is stirred until homogenous. Recrystallized urea (98 mg, 1.63 mmol) is added and the solution is stirred at room temperature for 5 minutes. 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester (0.54 mmol) is added, and the solution is heated to 80 °C for 30 minutes, then cooled to 50 °C and stirred for 16 hours. The reaction is then quenched by the addition of 10 mL water, and 1N hydrochloric acid is added to adjust the pH to 5. The aqueous layer is extracted with ethyl acetate (3 x 20

mL). The combined ethyl acetate layers are washed with saturated sodium chloride, dried with magnesium sulfate, filtered, and concentrated under vacuum to produce crude product. This material is chromatographed on silica gel (ISCO MPLC purification, 30 minutes, 50-100% ethyl acetate gradient, Biotage flash 40s column) to provide 1-[6-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione.

5 Preparation 1: 1-[6-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester

10 1-[6-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-yl]-pyrrolidine-2,2-dicarboxylic acid diethyl ester can be prepared by dissolving 2-[6-(Methyl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester (9.25 mmol) in dimethylformamide (90 mL), followed by addition of 1,3 dibromopropane (938 μ L, 9.25 mmol) and cesium carbonate (6 grams, 18.5 mmol). The reaction mixture is stirred for approximately 24 hours to 48 hours. The mixture is filtered through celite, and then concentrated under vacuum while heating to 55 °C to remove the dimethylformamide (azeotroping with toluene). The crude product obtained is chromatographed on silica gel (ISCO MPLC purification, 40 minutes, 0-50% ethyl acetate gradient, Biotage flash 40m column) to provide the title compound.

15 Preparation 2: 2-[6-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester

20 2-[6-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-ylamino]-malonic acid diethyl ester can be prepared by combining 5-(5-Amino-pyridin-2-yloxy)-1-methyl-1H-indazole (11.4 mmol), bromodiethylmalonate (11.4 mmol), and N,N-dimethylaniline (11.4 mmol) in a flame dried flask and heated to 70 °C for 3.5 hours. The mixture is cooled to room temperature, adsorbed to silica gel and chromatographed (gradient elution, ethyl acetate-hexanes) to afford the title compound.

25 Preparation 3: 5-(5-Amino-pyridin-2-yloxy)-1-methyl-1H-indazole

30 To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1-methyl-1H-indazole (0.79 mmol) in 10 mL of methanol was added 10 mL of ethyl acetate and 30 mg of platinum (IV) oxide. After shaking under 50 psi of H₂ for 3 h, the mixture was filtered through a pad of Celite and concentrated *in vacuo*, affording 0.25 g of 5-(5-Amino-pyridin-2-yloxy)-1-methyl-1H-indazole.

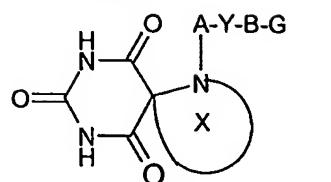
35 Preparation 4: 5-(5-Nitro-pyridin-2-yloxy)-1-methyl-1H-indazole

35 To a solution of 5-(5-Nitro-pyridin-2-yloxy)-1H-indazole (1.0 g, 3.9 mmol) in 15 mL of DMF is added sodium hydride (3.9 mmol) and methyl iodide (20 mmol). The resulting mixture is stirred at room temperature to 50 °C for 1-6 hours. The mixture is diluted with water, extracted 3x with ethyl acetate, and the combined organic layers are dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification by column chromatography eluting with ethyl acetate-hexanes, affords 5-(5-Nitro-pyridin-2-yloxy)-1-methyl-1H-indazole.

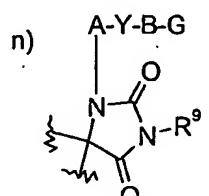
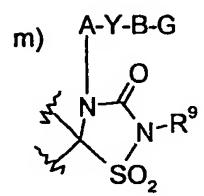
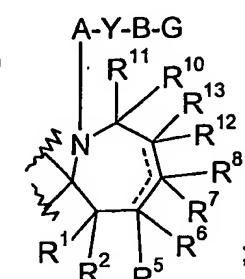
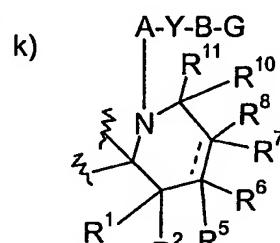
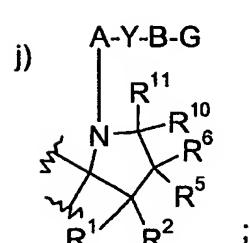
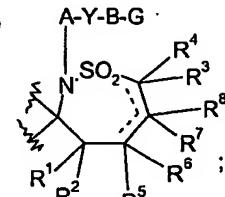
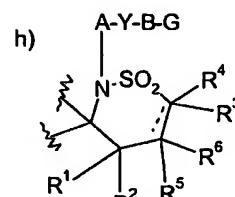
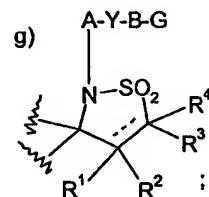
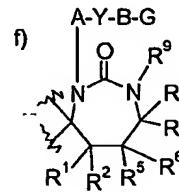
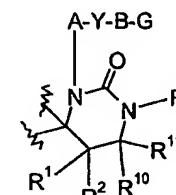
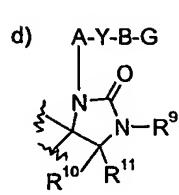
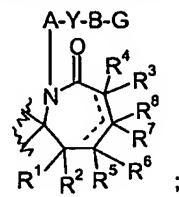
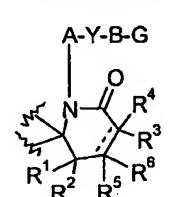
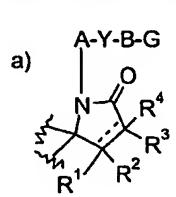
While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For 5 example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present 10 pharmaceutical carriers, as well as the type of formulation and mode of administration employed and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

We Claim:

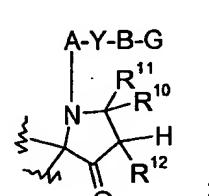
1. A compound of the formula:



wherein said ring X is a 5-7 membered heterocyclic ring selected from the group consisting of:



and



wherein each dashed line represents an optional double bond;

wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} is independently selected from the group consisting of hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, (C_6 - C_{10})aryl, (C_1 - C_{10})heteroaryl, (C_3 - C_8)cycloalkyl and (C_1 - C_{10})heterocyclyl;

5 wherein each of said R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} (C_1 - C_4)alkyl, (C_6 - C_{10})aryl, (C_1 - C_{10})heteroaryl, (C_3 - C_8)cycloalkyl and (C_1 - C_{10})heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent with one to three substituents per ring independently selected from halo, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, -CN, -OH and -NH₂;

10 wherein each of said R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} (C_1 - C_{10})heteroaryl and (C_1 - C_{10})heterocyclyl may optionally be substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C_1 - C_4)alkyl and (C_1 - C_4)alkyl-(C=O)-;

A is (C_6 - C_{10})aryl or (C_2 - C_{10})heteroaryl;

15 wherein said may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy and (C_3 - C_8)cycloalkyloxy;

20 Y is selected from the group consisting of a bond, -O-, -S-, >C=O, >SO₂, >S=O, -CH₂O-, -OCH₂-, -CH₂S-, -SCH₂-, -CH₂SO-, -CH₂SO₂-, -SOCH₂-, -SO₂CH₂-, >NR¹⁴, -[N(R¹⁴)]CH₂-, -CH₂[N(R¹⁴)]-, -CH₂-, -CH=CH-, -C≡C-, -[N(R¹⁴)]-SO₂- and -SO₂[N(R¹⁴)]-;

25 R¹⁴ is selected from the group consisting of hydrogen and (C_1 - C_4)alkyl;

B is a heterocyclyl containing at least one nitrogen atom;

wherein one ring nitrogen atom of B is bonded to one carbon atom of G;

25 with the proviso that the group -B-G cannot be methylazetidinyl or methylpiperidinyl;

wherein said B may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one or two substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)alkyl, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, (C_3 - C_8)cycloalkyloxy, (C_6 - C_{10})aryl, (C_3 - C_8)cycloalkyl, (C_1 - C_{10})heteroaryl and (C_1 - C_{10})heterocyclyl;

30 G is (C_1 - C_6)alkyl or R¹⁵-(CR¹⁶R¹⁷)_p;

p is an integer from zero to four;

wherein said G (C_1 - C_6)alkyl may be optionally substituted on any of the carbon atoms capable of supporting an additional substituent by one to three substituents per (C_1 - C_6)alkyl independently selected from F, Cl, Br, CN, OH, (C_1 - C_4)perfluoroalkyl, (C_1 - C_4)perfluoroalkoxy, (C_1 - C_4)alkoxy, -NH₂, (C_1 - C_4)alkyl-NH-, [(C_1 - C_4)alkyl]₂-N- and (C_3 - C_8)cycloalkyloxy;

R^{15} is selected from the group consisting of (C_3-C_8) cycloalkyl, (C_6-C_{10}) aryl, (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl;

wherein each of said R^{15} (C_6-C_{10}) aryl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl may be optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, -NH₂, (C_1-C_4) alkyl-NH-, $[(C_1-C_4)$ alkyl]₂-N- and (C_3-C_8) cycloalkyloxy;

wherein each of said R^{15} (C_3-C_8) cycloalkyl and (C_1-C_{10}) heterocyclyl may also 10 optionally be substituted by oxo;

wherein each of said R^{15} (C_1-C_{10}) heteroaryl and (C_1-C_{10}) heterocyclyl may optionally be substituted on any ring nitrogen atom able to support an additional substituent independently selected from the group consisting of (C_1-C_4) alkyl and (C_1-C_4) alkyl-(C=O)-;

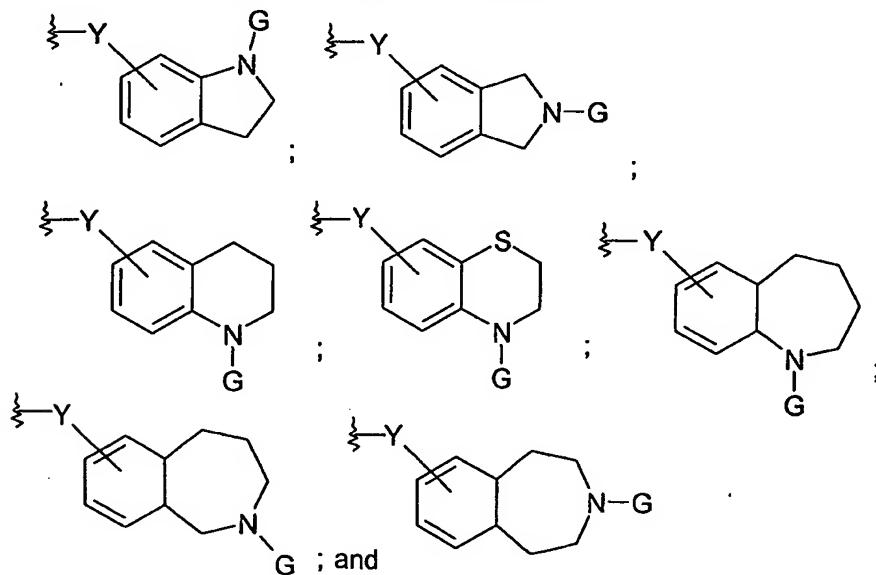
each of R^{16} and R^{17} are independently selected from the group consisting of hydrogen 15 and (C_1-C_4) alkyl;

or R^{16} and R^{17} may optionally be taken together with the carbon to which they are attached to form a 3 to 8-membered carbocyclic ring;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein B is a monocyclic saturated (5- to 20 7-membered)-heterocyclic ring containing at least one ring nitrogen atom fused to an aromatic six membered ring.

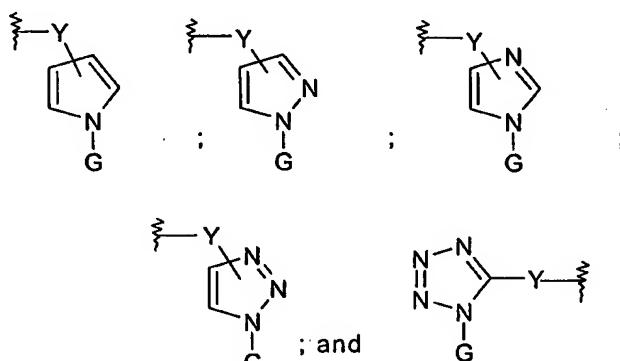
3. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of



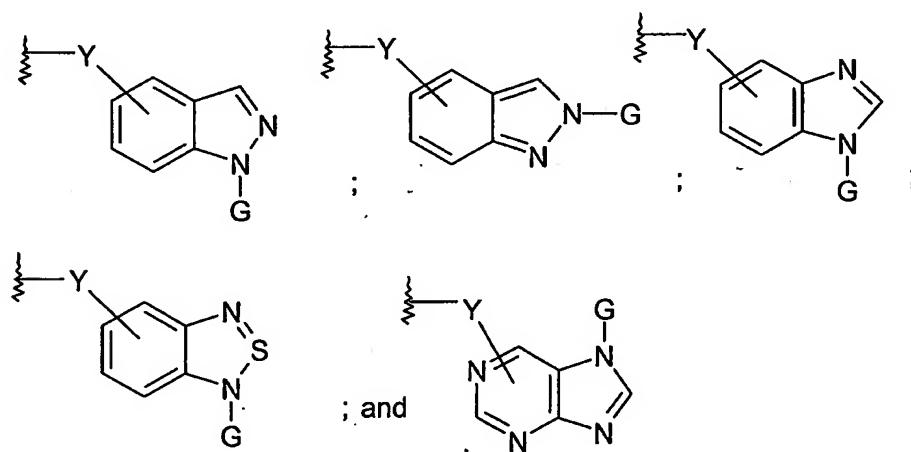
4. A compound according to any of the preceding claims wherein B is selected from the group consisting of a monocyclic partially saturated (5- to 7-membered)-ring containing at least one nitrogen atom; a partially saturated (5- to 7-membered)-heterocyclic ring containing at least one nitrogen atom fused to an aromatic six membered ring; a 5 monocyclic aromatic (5- to 6-membered)-heterocyclic ring containing at least one nitrogen atom; an aromatic (5- to 6-membered)-ring containing at least one nitrogen atom fused to an aromatic six membered ring.

5. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of

10



6. A compound according to any of the preceding claims wherein the group -Y-B-G has the formulae selected from the group consisting of



7. The compound according to any of the preceding claims wherein said G is selected from the group consisting of (C₁-C₆)alkyl; -[R¹⁵-(CR¹⁶R¹⁷)_p]-, wherein p is zero; and -[R¹⁵-(CR¹⁶R¹⁷)_p]-; wherein p is an integer from one to four.

8. The compound according to any of the preceding claims wherein R¹⁵ is selected from the group consisting of (C₃-C₈)cycloalkyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per

ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein said R¹⁵ (C₃-C₈)cycloalkyl may also optionally be substituted by oxo; (C₆-C₁₀)aryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; (C₁-C₁₀)heteroaryl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; (C₁-C₁₀)heterocyclyl optionally substituted on any of the ring carbon atoms capable of supporting an additional substituent by one to three substituents per ring independently selected from F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, -NH₂, (C₁-C₄)alkyl-NH-, [(C₁-C₄)alkyl]₂-N- and (C₃-C₈)cycloalkyloxy; and wherein said (C₁-C₁₀)heterocyclyl may also optionally be substituted by oxo.

9. A compound according to any of the preceding claims wherein Y is -O-.

10. A compound according to any of the preceding claims wherein A is optionally substituted (C₆-C₁₀)aryl; or optionally substituted (C₁-C₁₀)heteroaryl; wherein said (C₆-C₁₀)aryl; or (C₁-C₁₀)heteroaryl is optionally substituted on any ring carbon atom capable of supporting an additional substituent by one or two substituents per ring independently selected from the group consisting of F, Cl, Br, CN, OH, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)alkoxy, and (C₃-C₇)cycloalkyloxy.

25 11. A compound according to claim 1, wherein said compound is selected from the group consisting of:

1-[6-(1-Isopropyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-(2-Isopropyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-2-yl]-benzonitrile

1-[6-[2-(2-Hydroxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

40 1-[6-[2-(2-Ethoxy-ethyl)-1-oxo-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

45 1-[6-[2-(4-Fluoro-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-(2-Pyridin-3-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Fluoro-phenyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(1-Pyridin-3-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Fluoro-phenyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(1-Pyridin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Fluoro-phenyl)-1H-benzimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-[1-(4-Fluoro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

6-[7-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl]-nicotinonitrile;

25 6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3-dihydro-indol-1-yl]-nicotinonitrile;

1-[6-(2-Pyridin-3-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 6-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-2H-quinolin-1-yl]-nicotinonitrile;

1-[6-(1-Pyridin-4-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(1-Pyridin-3-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

6-[6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-1H-isoquinolin-2-yl]-nicotinonitrile;

35 6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-1,3-dihydro-isoindol-2-yl]-nicotinonitrile;

6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-1-yl]-nicotinonitrile;

6-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-2-yl]-nicotinonitrile;

1-[6-(2-Pyridin-4-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-(1-Pyridin-4-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-4-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(2-Pyridin-3-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-4-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(1-Pyridin-3-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-4-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-(2-Pyridin-4-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-3-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-(2-p-Tolyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-p-Tolyl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-[2-(4-Chloro-phenyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(4-Chloro-phenyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(2-Pyridin-2-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridin-2-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[2-(3-Methoxy-propyl)-2H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(2-Pyridazin-3-yl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-(1-Isopropyl-1H-benzoimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(2-Isopropyl-2H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(2-Pyridin-2-yl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-(2-Isopropyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-(2-Pyridin-3-yl-2,3-dihydro-1H-isoindol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-[2-(3-Methoxy-propyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-[2-(3-Methoxy-propyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(3-Methoxy-propyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Isopropyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

40 1-[6-(2-p-Tolyl-1,2,3,4-tetrahydro-isoquinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

45 4-[5-[6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl]-pyridin-2-yloxy]-indazol-2-yl-benzonitrile;

1-{6-[1-(4-Methoxy-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-{6-[2-(4-Chloro-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 4-{6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-1H-isoquinolin-2-yl}-benzonitrile;

4-{5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3-dihydro-indol-1-yl}-benzonitrile;

10 1-{6-[1-(4-Methoxy-phenyl)-1H-benzoimidazol-5-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-{6-[2-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 4-{6-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-3,4-dihydro-2H-quinolin-1-yl}-benzonitrile;

1-{6-[1-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 4-{7-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-benzonitrile;

4-{5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-1,3-dihydro-isoindol-2-yl}-benzonitrile;

1-{6-[1-(4-Chloro-phenyl)-1,2,3,4-tetrahydro-quinolin-6-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-p-Tolyl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 4-{5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-benzoimidazol-1-yl}-benzonitrile;

1-{6-[1-(3-Methoxy-propyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-{6-[1-(4-Chloro-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy]-pyridin-3-yl}-30 1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-p-Tolyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-{6-[2-(4-Methoxy-phenyl)-2,3-dihydro-1H-isoindol-5-yloxy]-pyridin-3-yl}-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(1-Pyridazin-3-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-1,2,3,4-tetrahydro-quinolin-6-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

4-[5-[5-(6,8,10-Trioxo-1,7,9-triaza-spiro[4.5]dec-1-yl)-pyridin-2-yloxy]-indazol-1-yl]-benzonitrile;

1-[6-(1-p-Tolyl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

5 1-[6-[1-(4-Methoxy-phenyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridazin-3-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

10 1-[6-(1-Pyridazin-3-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridazin-3-yl-1H-indazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

15 1-[6-(1-Pyridin-2-yl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-(1-Pyridin-2-yl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

20 1-[6-[1-(4-Methoxy-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Chloro-phenyl)-1H-benzimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

25 1-[6-[1-(3-Methoxy-propyl)-1H-benzimidazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(3-Methoxy-propyl)-2,3-dihydro-1H-indol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

30 1-[6-[1-(4-Chloro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

1-[6-[1-(4-Chloro-phenyl)-1H-indazol-5-yloxy]-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

35 1-[6-(1-p-Tolyl-1H-benzimidazol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione; and

1-[6-(1-p-Tolyl-2,3-dihydro-1H-indol-5-yloxy)-pyridin-3-yl]-1,7,9-triaza-spiro[4.5]decane-6,8,10-trione;

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition for the treatment of a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, 5 reproductive health disorders, gastric disorders, skin disorders and cancers in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

13. A method for treating a condition selected from the group consisting of connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious 10 diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

15 14. A pharmaceutical composition for the treatment of a condition which can be treated by the inhibition of matrix metalloproteinases in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

15. A method for the inhibition of matrix metalloproteinases in a mammal, 20 including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/01508

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D487/10 A61K31/505 A61P37/00 A61P29/00 A61P19/02
 //((C07D487/10, 239:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 12611 A (BLAGG JULIAN ;PFIZER PROD INC (US)) 22 February 2001 (2001-02-22) claim 2; examples; table 1	1-15
P,A	WO 02 34753 A (BRONK BRIAN SCOTT ;WYTHES MARTIN JAMES (US); NOE MARK CARL (US); P) 2 May 2002 (2002-05-02) claims; example 12	1-15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

31 July 2003

08/08/2003

Name and mailing address of the ISA

Authorized officer

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax. (+31-70) 340-3016

Härtinger, S

INTERNATIONAL SEARCH REPORT**PCT/IB 03/01508****Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13 and 15 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IB 03/01508

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0112611	A 22-02-2001	AU	6010500 A	13-03-2001
		BG	106406 A	30-09-2002
		BR	0013081 A	23-04-2002
		CA	2381551 A1	22-02-2001
		CN	1368963 T	11-09-2002
		CZ	20020355 A3	17-07-2002
		EE	200200069 A	15-04-2003
		EP	1202974 A1	08-05-2002
		HU	0202501 A2	28-12-2002
		WO	0112611 A1	22-02-2001
		JP	2003507371 T	25-02-2003
		NO	20020662 A	09-04-2002
		NZ	516562 A	30-06-2003
		SK	1652002 A3	10-09-2002
		TR	200200381 T2	21-05-2002
		US	6579982 B1	17-06-2003
WO 0234753	A 02-05-2002	AU	1081302 A	06-05-2002
		BR	0114913 A	01-07-2003
		CA	2425283 A1	02-05-2002
		WO	0234753 A2	02-05-2002
		US	2003096803 A1	22-05-2003